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ARCHIVES OF OPHTHALMOLOGY

VOLUME 35 (old series Volume 92) FEBRUARY 1946 NUMBER 2

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A BASKET TYPE IMPLANT FOR USE AFTER ENUCLEATION

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THIS is a preliminary report on a new type of implant for use in enucleation procedures. It is designed to impart more rapid movement to the prosthesis and to reduce the possibility of postoperative complications.

The history of evisceration and enucleation has recently been reviewed by Dimitry.[1] Although there are surgeons who still do not use an implant of some form, either in the sclera or in Tenon's capsule, the majority today consider that a more adequately filled socket and a better functioning stump are obtained with an implant. Here there is diversity of opinion as to the material, the shape and the method of implantation.

It is a common observation that whether an evisceration or an enucleation with implantation has been done there is fairly good movement of the stump. This is true whether the rectus muscles have been sutured together or not. In fact, often surprisingly good movement in the socket is obtained with a simple enucleation. The problem has been to transmit the movement to the prosthesis. Its solution has been aided by the recent development of molded plastic artificial eyes, which give a better contact with the socket, resulting in increased movement.

It was with the idea of providing the socket with a better grip on the prosthesis that a new type of basket implant was devised to be placed in Tenon's capsule. This basket implant has been in routine use for several months in an Army general hospital designated as an eye center. During that time 50 enucleations have been done by eight different ophthalmologists using this type of implant. A study has been made of the size and shape of the basket, the operative procedure and the final prosthesis. Although this work is being continued and extended, it is felt that sufficient standardization has been attained that a preliminary report may be made.

The purpose of a basket implant, with a resulting depressed area in the socket, is to give the prosthesis, which has a stud projecting pos-

1. Dimitry, T. J.: The Socket After Enucleation and the Artificial Eye, Arch. Ophth. **31**:18 (Jan.) 1944.

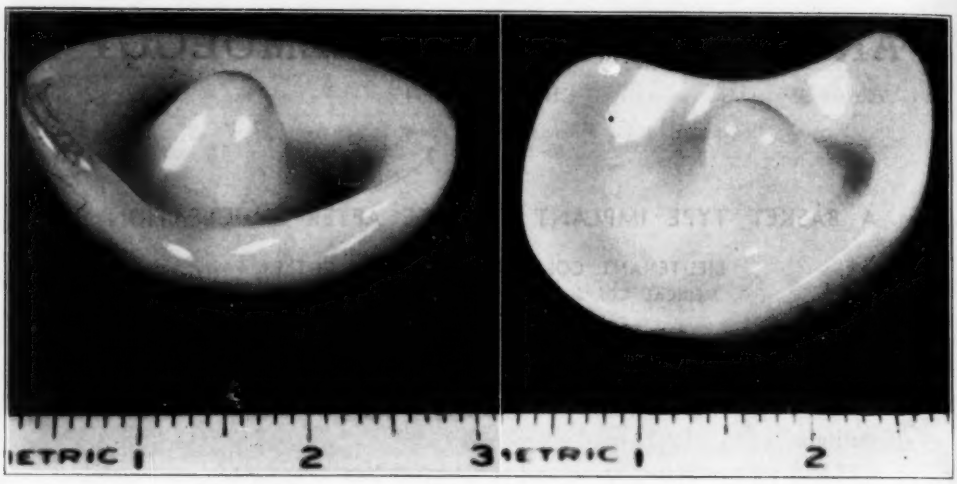

Fig. 1.—Plastic prosthesis, showing projecting stud on the posterior surface.

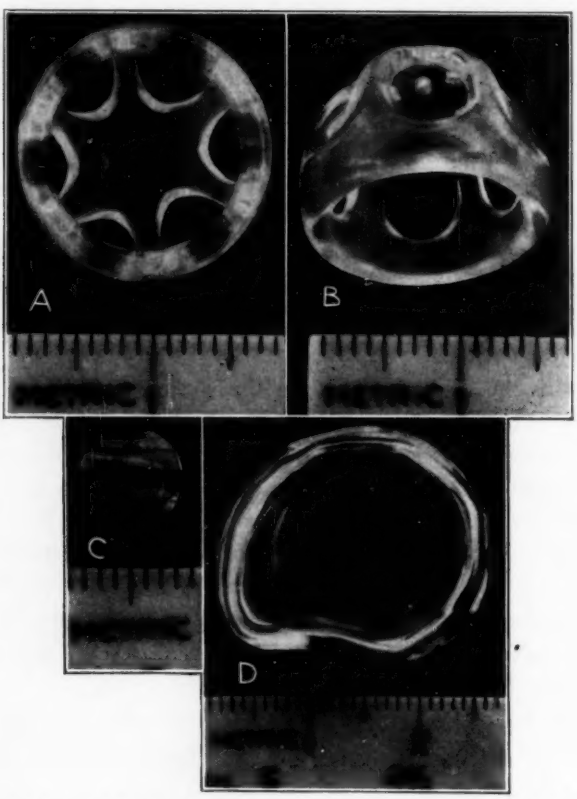

Fig. 2.—*A*, view of Lucite basket from above; *B*, lateral view of the basket; *C*, Lucite stud, and *D*, posterior view of Lucite basket with central depression for stud.

teriorly (fig. 1), a grip on the stump. This necessitates, of course, a custom-designed prosthesis and, in addition, imposes new problems of design on the artificial eye maker. This is due to the fact that there is more ability of the cuplike depression to move the artificial eye than there is space in which the eye can move. Thus, it is necessary to adjust carefully the size and shape of the prosthesis in order to use the minimum amount of space and still maintain a normal fissure. This is facilitated if no attempt is made to fill out a depressed upper lid with the prosthesis, but that is left to the surgeon.

The standard basket now used is shown in figure 2 *A* and *B*. It is made of Lucite (methyl methacrylate) and measures 11 by 15 mm. This size seems to be the best whether the eye to be enucleated is large or small. The anterior edge is slightly thickened. As shown in figure 2 *A* and *B*, the sides of the basket are fenestrated to allow for invasion of tissue. In addition, there are three holes in the bottom, measuring 1 mm. in diameter, two of which are for sutures. Larger and smaller baskets have been tried, but a tendency to reduce movement has resulted in either case. Other materials are being tried, but Lucite has been found satisfactory up to the present time. The situation after several years will still have to be determined. A Lucite button, measuring 5 by 8 mm., with four 0.8 mm. holes (fig. 2 *C*) is used to tie the sutures through and maintain the depression during healing. Three double-armed sutures are used: black 0 nylon, blue 00 dermal and purple coarse dermal. These are used because of their greater strength and smoothness, allowing sutures to be pulled up without breaking. They are of different colors to permit ready identification. One inch (2.5 cm.) straight intestinal needles are used to allow their passage through the plastic button.

At the end of the operation a special plastic retainer (fig. 2 *D*) is placed inside the lids after the method of Gifford.[2] This greatly reduces postoperative edema, keeps the basket centered and completely prevents any prolapse of the conjunctiva. The average operating time for this procedure is the same as for any implantation procedure, namely, twenty-two to twenty-five minutes.

Two baskets slightly smaller than the standard have been placed inside the sclera after evisceration. No advantage accrued as far as movement of the stump was concerned, and the depression into which the stud of the prosthesis fits was considerably smaller. In addition, there was extreme postoperative edema, involving the entire side of the face, which lasted seven to ten days. I have seen 2 cases in which a ball implant was placed in the sclera with extremely good movement, prac-

2. Gifford, S. R.: Plastic Shell for Use in Simple Enucleation of Globe, Arch. Ophth. **30**:775 (Dec.) 1944.

tically as good as that of the normal eye, but because of the smooth contour only a small amount could be transmitted to the prosthesis.

Many enucleation procedures and implants have been devised to insure action of the ocular muscles, by suturing them in front of the prosthesis or to the prosthesis itself. It is my opinion, as previously stated that the problem of motion of the prosthesis does not lie in this solution. In fact, in the procedure to be described, no attention is paid to attachment of muscles at all. Figure 3 shows the posterior view of a basket implant removed at autopsy eight and one-

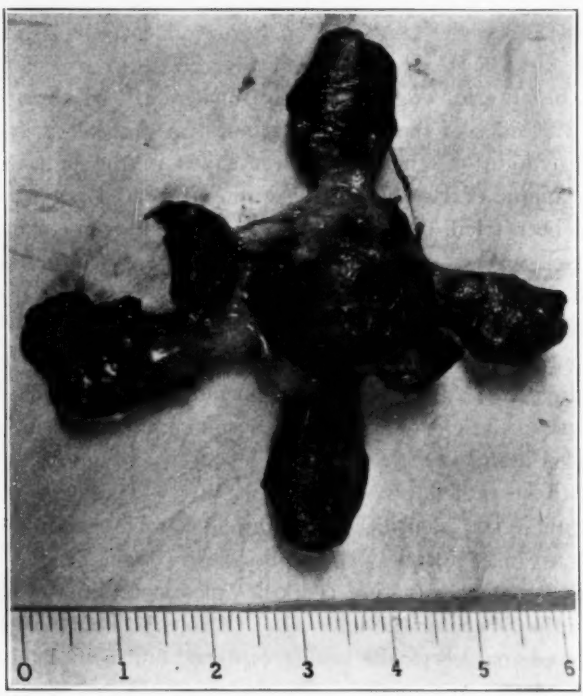

Fig. 3.—Posterior view of basket implant removed at autopsy eight months after implantation, showing muscles attached to the anterior edge.

half months after operation from a patient who was killed in an automobile accident. It will be seen that all the muscles, including the oblique, are attached at or near the rim of the basket.

OPERATIVE PROCEDURE

Anesthesia is induced by intravenous injection of sodium pentothal and retrobulbar injection of 2 cc. of 2 per cent procaine hydrochloride.

The eye is prepared in the usual manner. A speculum (Weeks) is inserted, the conjunctiva dissected from the limbus and the dissection

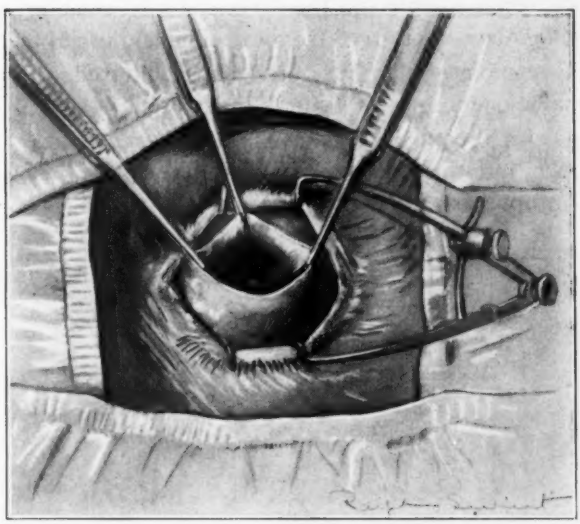

Fig. 4—Tenon's space exposed, ready for insertion of the basket implant.

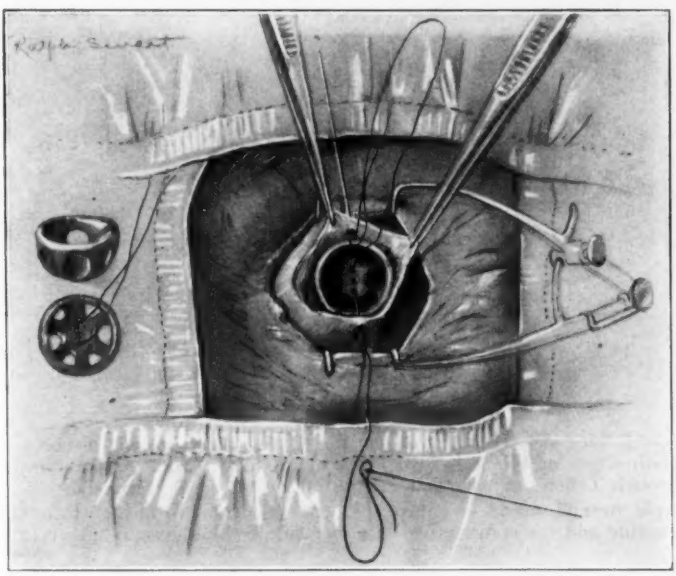

Fig. 5.—Basket with black 0 nylon suture inserted. The suture is carried through Tenon's capsule and the conjunctiva at 12 and 6 o'clock.

carried to the fornices in all directions. The rectus muscles are then isolated and cut free from their insertions. The conjunctival opening usually is enlarged nasally and temporally about 2 mm. to permit passage of the globe. The globe is grasped with fixation forceps at the tendon

of the internal rectus muscle and the nerve cut with enucleation scissors. The prolapsed globe is then freed from the oblique muscles and removed.

A dry gauze sponge and a little pressure usually reduce the bleeding quickly to enable one to inspect Tenon's capsule (fig. 4).

The basket, with one black nylon suture, size 0, fitted with two straight 1 inch intestinal needles, is then placed in Tenon's capsule (fig. 5). The upper suture is brought through a firm bite of Tenon's

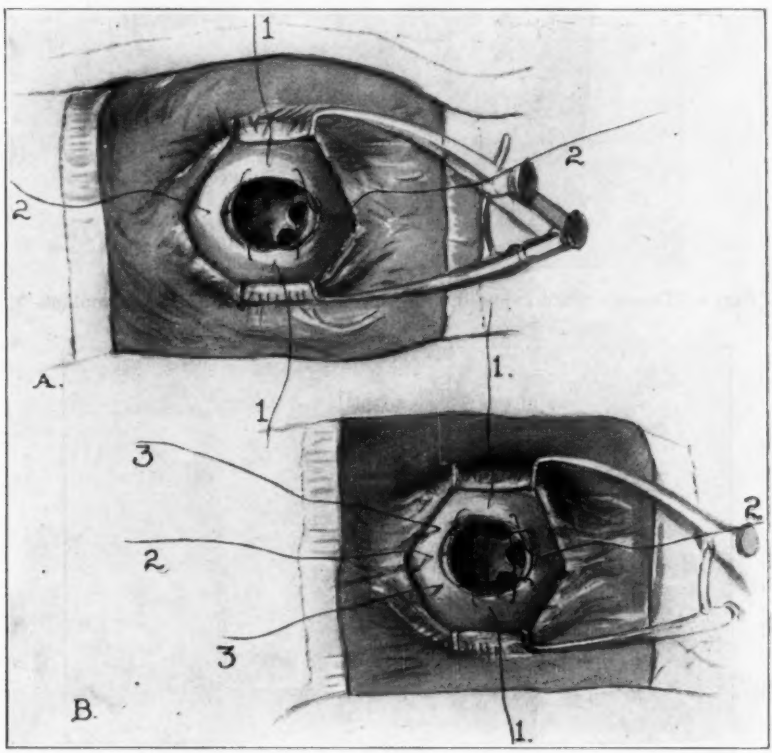

Fig. 6.—*A*, blue dermal mattress suture (*2*) carried through Tenon's capsule and the conjunctiva on either side of black nylon suture from within outward and, finally, through Tenon's capsule and the conjunctiva at 3 and 6 o'clock.

B, purple dermal mattress suture (*3*) carried from within outward through Tenon's capsule and the conjunctiva on either side of blue dermal suture (*2*).

capsule at 12 o'clock and out through the margin of the conjunctiva. The lower suture is brought out similarly at 6 o'clock.

A blue 00 dermal, double-armed suture with a 1 inch intestinal needle is then carried through Tenon's capsule and the conjunctiva about 2 mm. on either side of the black suture which was placed at 6 o'clock (fig. 6*A*). Each suture is then carried through in a similar manner at 12 o'clock. The suture on the right side is now carried through Tenon's

capsule and the conjunctiva at 3 o'clock on the same side, and the suture on the left, at 9 o'clock.

A purple dermal (coarse), double-armed suture, similar to the blue dermal suture, is now placed about 2 mm. on either side of the blue suture at 3 o'clock, the needle taking similar bites of Tenon's capsule and coming out through the conjunctiva. These two sutures are now

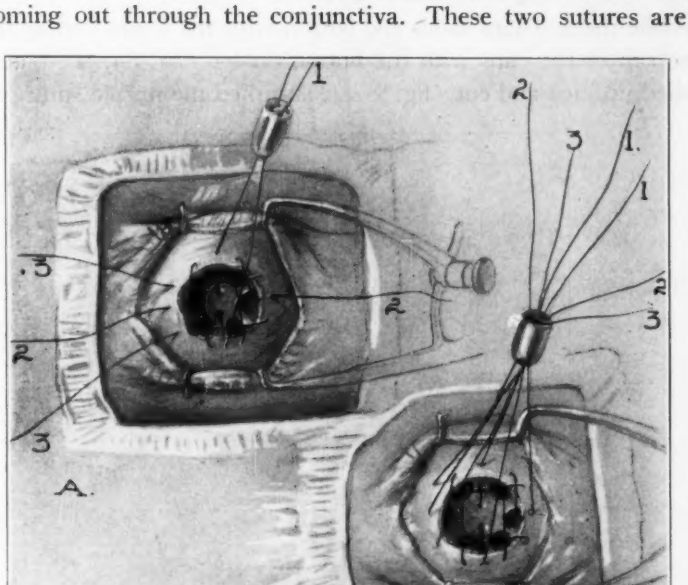

Fig. 7.—Black nylon suture (*1*) carried through holes in the Lucite stud. *B*, purple dermal suture (*3*) carried through the same holes in the stud as suture *1*; blue dermal suture (*2*) carried through the other two holes in the Lucite button.

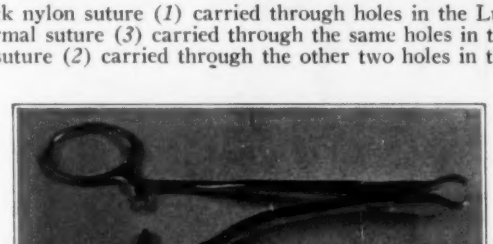

Fig. 8.—Button holder.

carried across above all other sutures and brought out 2 mm. on either side of the blue suture at 9 o'clock (fig. 2 *B*).

These two mattress sutures (blue and purple) are placed as outlined in the preceding paragraphs, so that when they are pulled up they cause

a double imbrication, or folding, of Tenon's capsule and the conjunctiva and the black sutures still come out through the upper layer after this has been done. All sutures are carried through the Lucite stud, as shown in figure *7 A* and *B*. Sutures *1* and *3* pass through the same two holes and suture *2* through the other two holes.

While the assistant holds the button with the lower end at the level of the rim of the cups with the button holder (fig. 8), the blue suture is pulled up, tied and cut (fig. 9 *A*), and then the purple suture is simi-

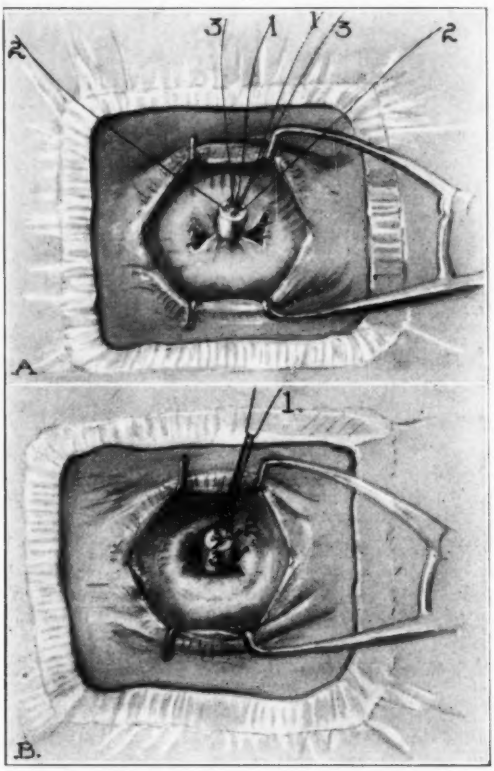

Fig. 9.—*A*, suture (*2*) pulled up, imbricating Tenon's capsule and the conjunctiva vertically.

B, suture *2* tied and cut; suture *3* pulled up tight and cut through, imbricating Tenon's capsule and the conjunctiva horizontally and closing the basket opening.

larly handled. This pulls Tenon's capsule and the conjunctiva into place and closes the opening.

A single tie is now placed in the black suture, and as this tie is gradually pulled up the index fingers make traction and a little pressure. The assistant then releases the button from the forceps. As this tie is pulled tight, it forces the button with Tenon's capsule and the conjunctiva down

into the cup. Three knots are placed and the suture cut (fig. 10). No conjunctival sutures are necessary.

A Lucite retainer is placed inside the lids. An adhesive dressing with firm pressure but with no roller bandage is applied.

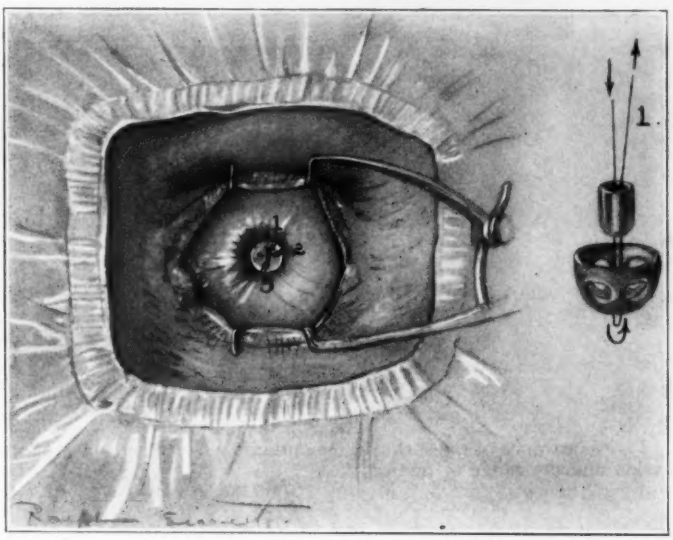

Fig. 10.—Suture (*1*) pulled up, tied and cut, forcing button with Tenon's capsule and conjunctiva down into the basket.

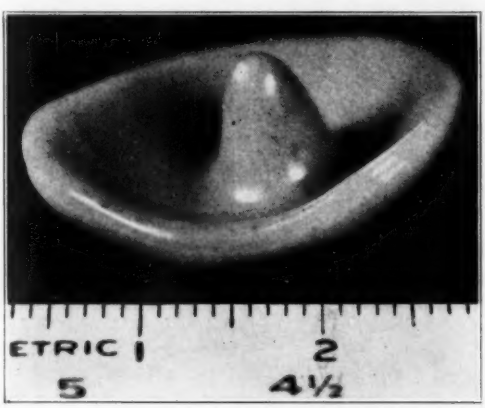

Fig. 11.—Plastic retainer.

POSTOPERATIVE COURSE

The first dressing is done on the third postoperative day, the retainer being removed and the socket irrigated. The retainer is replaced, and if

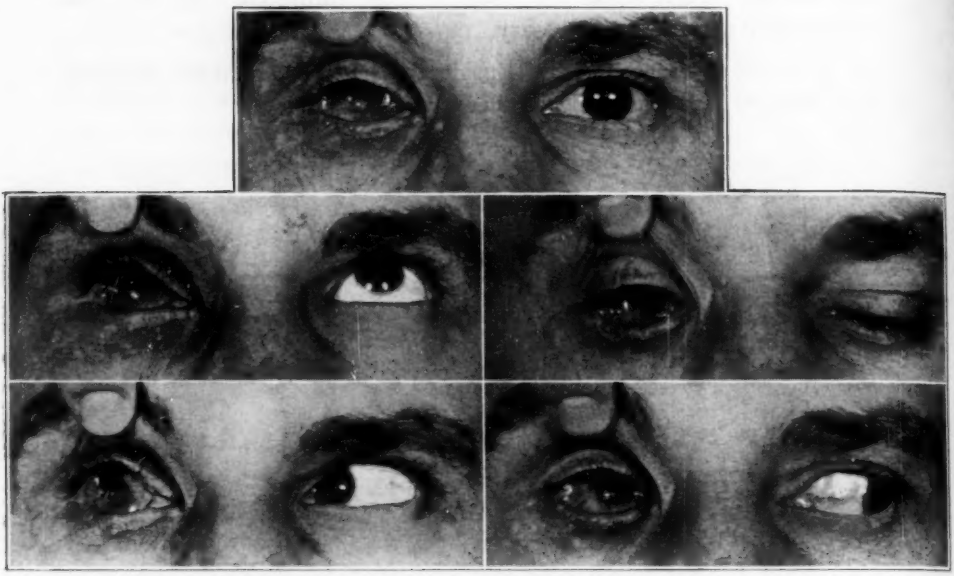

Fig. 12.—Appearance of the socket one month after operation, showing impression in the basket and the range of motion.

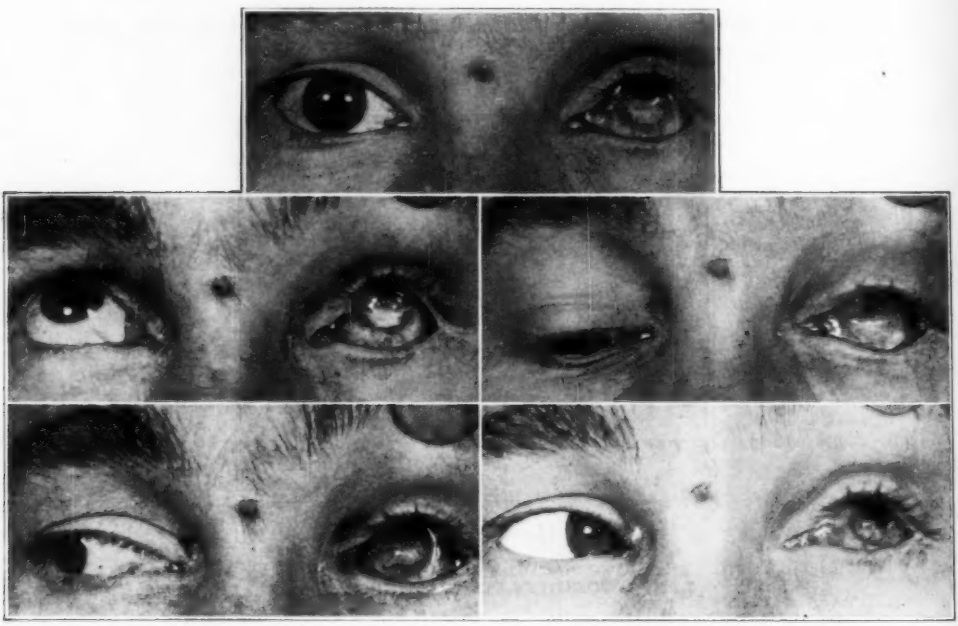

Fig. 13.—Appearance five months after operation, showing depression and movement of the socket.

there is still some edema an adhesive dressing is put back on for two more days. In most cases the dressing can be omitted. On the fifth postoperative day the sutures and the button are removed. A temporary retainer with button attached (fig. 11) is placed in the socket at this time. This is removed daily, and the socket is irrigated for a week.

In none of the cases in which operation was performed has there been any prolapse of the conjunctiva. This is probably due to the type of operation and to the retainer. In general, there has been little reaction and no discomfort at all after the first postoperative day.

At the end of two to three weeks, depending on the shrinkage of its tissues, the socket is ready for a custom-made prosthesis, similar to the one shown in figure 1.

COMPLICATIONS

It is important not to pull the sutures beyond the snug state, as otherwise pressure necrosis and exposure of the bottom of the basket will result. This complication will also occur if the button is not removed at the end of five days. If exposure of the bottom of the basket does occur, a retainer without a button attached is put in, and granulation and epithelization will take place in a few days, without impairment of the result. If, after the sutures and the button are removed on the fifth postoperative day, there is a thin-appearing lining on the bottom of the basket, a plain retainer can be used from one to three days and then a button retainer employed.

A sufficiently firm bite of Tenon's capsule must be obtained in placing the mattress sutures, since there is slight tension on the capsule when it is inverted into the basket. In 2 cases in which a ball implant was removed and a basket put in the sutures did not hold. This was also true in a case in which a considerable amount of scar tissue was present—the sutures cut through the inelastic scar tissue. It was necessary in these 3 cases to remove the baskets.

Postoperative hemorrhage has never been a problem in our cases. In the 3 cases just mentioned, in which the sutures did not hold because of scar tissue and the basket was removed approximately ten days after operation, it had to be dissected out. Certainly, the basket cannot be extruded.

PROSTHESIS

The socket is ready for the final prosthesis at the end of two or three weeks. This has been of plastic, made according to the standard Army procedure and under the direction of Capt. Stanley F. Erpf and Capt. Arthur L. Lundblad of the Dental Corps of the Army of the United States.

The prosthesis is not made from an impression of the socket, since that would result in its occupying too much of the available space. Figure

1 shows some variations in the prostheses that have been fitted. In general, the stud is adjusted to fit into the depression, and the base around this stud is cut away to allow the edge of the basket to come forward when the socket is turned. Through support of the stud, there is considerable relief of pressure on the tissues in the region of the fornices.

It is not absolutely necessary to use a custom-made eye with a stud; good movement can often be obtained with a Snellen form. The reason for this is that the movement of the prosthesis is in part due to the change in the shape of the socket when the basket rotates; one side becomes shallow and the opposite side deep, and the eye has to move.

The following tabulations were made on the basis of observations on 60 sockets fitted with artificial eyes. Practically all of them were fitted with custom-made plastic eyes. It is realized that this small number may not represent a true cross section. The series was collected from the wards without regard to the preoperative condition. It consisted of 20 sockets without implants, 20 with ball implants and the first 20 with basket implants.

Average Motion Degrees	No Implant	Ball Implant	Basket Implant
Nasally	19	19	28
Temporally	13	15	22
Superiorly	25	20	29
Inferiorly	12	20	30
Total	69	74	109

The sockets without implants showed the greatest variation in movement from patient to patient and those with basket implants the least variation. This is illustrated by the following tabulation:

Prostheses Having:	No Implant	Ball Implant	Basket Implant
45° total horizontal movement	1 of 20	3 of 20	18 of 20
50° total vertical movement	6 of 20	8 of 20	19 of 20

It is felt that with more study of the most desirable shape for the prostheses, the statistics on the results of basket implantation will be further improved. These tabulations do not indicate the action of the oblique muscles, which is a prominent feature of the basket sockets. Neither do they indicate the most important characteristic of all, that is, the much more rapid response to movement of the muscle cone, with a notable decrease in the time lag as compared with that for the normal eye. The movement with this method comes more nearly within the average range of normal action than that with any previous procedure.

SUMMARY

On the basis of 50 operative procedures, a new type of basket implant for use after enucleation is presented which, with a new type of pros-

thesis, gives more instantaneous movement and a wider range of action. This procedure, combined with use of a plastic retainer, eliminates prolapse of the implant and shortens the period of postoperative convalescence.

Mr. Ralph Sweet contributed the drawings; Capt. Stanley Erpf D. C., and Capt. Arthur L. Lundblad, D. C., A. U. S., modified and adapted the plastic prosthesis, and Corporal Cheetham, dental technician, helped in developing a technic for making the baskets.

1300 Harrison Street, Wilmington, Del.

UVEAL BLASTOMYCOSIS

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SOUTH BEND, IND.

MY interest in blastomycosis of the eye was incited by a patient who recently came under by observation. A review of the ophthalmic literature reveals only a meager contribution to the subject of fungous disease of the eye. Aspergillosis has been reported as penetrating the eye from a necrotic ulcer. Actinomycosis has occasionally been reported as an intraocular infection, and experimental metastatic infection of the eye has been demonstrated after intravenous injection of fungus in animals.[1] From this evidence, and from a few case reports not cited here, one may conclude that metastatic uveitis in association with systemic blastomycosis is not as unusual as it seems.

The name "blastomycosis" has often been declared a misnomer. The confusion results from the discrepancy between the American interpretation and the broader classification of a group of closely related diseases caused by yeastlike, or budding, fungi. The North American disease is a special type, known as "Gilchrist's disease." Cultural studies of North American and South American blastomycosis [2] show that the fungi in the two diseases are sufficiently similar to be placed in the same genus—Blastomyces. Paracoccidioidal granuloma, or South American blastomycosis, is caused by one species, the Blastomyces brasiliensis, while Blastomyces dermatitidis is the etiologic agent in North American blastomycosis.

In 1898 Gilchrist and Stokes [3] described pseudo lupus vulgaris caused by a yeastlike organism which was nonfermenting and produced myceliums on artificial culture mediums. He called this causative fungus Blastomyces dermatitidis. The disease since then has often been called Gilchrist's disease, or blastomycosis. The organism is an oval, refractile body with thick walls and a double-contoured capsule.

In 1928 Castellani [4] pointed out that blastomycosis included all conditions caused by a yeastlike, or budding, fungus but that in the United

1. Duke-Elder, W. S.: Textbook of Ophthalmology, St. Louis, C. V. Mosby Company, 1941, vol. 3, p. 2367.

2. Howell, A., Jr., and Conant, N. F.: Similarity of Fungi Causing South American Blastomycosis (Paracoccidioidal Granuloma) and North American Blastomycosis (Gilchrist's Disease), J. Invest. Dermat. **5**:353 (Dec.) 1942.

3. Gilchrist, T. C., and Stokes, W. R.: A Case of Pseudo Lupus Vulgaris Caused by a Blastomyces, J. Exper. Med. **3**:53, 1898.

4. Castellani, A.: Blastomycosis and Some Other Conditions Due to Yeastlike Fungi (Budding Fungi), Am. J. Trop. Med. **8**:379 (Sept.) 1928.

States the term is used to denote a clinical entity characterized by the presence of granulomatous, verrucoid lesions in which fungi of the blastomycete type are found. Henrici [5] called the fungus in blastomycosis "Cryptococcus gilchristi," under the genus Oidium oidiomycosis. Jacobson,[6] in describing the mycology of Gilchrist's disease, stated that the causative agent is an encapsulated and budding organism represented by two species, Blastomyces immitis and B. dermatitidis, prevalent in and around Chicago. It grows widely and is found on vegetables of all sorts and on decaying wood. The organism is a budding yeast cell found in pus or in biopsy tissue after fixation. It is seen best unstained. Strong [7] pointed out that the organism is 7 to 20 microns in diameter, is encapsulated by a thick, highly refractile membrane, forms myceliums in culture and buds in tissue.

Stober,[8] in discussing the sources of infection, said that growth could be obtained on sterile moist bread, paper, cardboard, cotton, sawdust, fruit and vegetables. He had found the mold in damp wood in houses of patients with blastomycosis and cited scratch or injury from barbed wire while walking barefoot as a possible source of infection. Jacobson [6] stated that blastomycosis is a protean disease in its clinical manifestations. No organ in the body is immune. There are two types of blastomycosis, cutaneous and systemic. The systemic disease affects every organ in the body—skin, lungs, kidneys, spleen, bones, prostate gland and meninges, in about that order of incidence. The skin is often the focus from which it reaches the lungs, through the blood stream. The onset is often insidious, starting as a papilloulcerative, verrucous, papillomatous or gummatous lesion of the skin, which persists for years, resulting in subacute or chronic pyemia. The infection results in malaise, loss of weight and strength, emaciation, recurrent chills, night sweats and irregular fever. Involvement of the lungs, with single or multiple pulmonary abscesses, often occurs. The diagnosis depends on finding the causative organism, in pus, in the secretions or in fixed biopsy tissue. The differential diagnosis must exclude tuberculosis, coccidioidal granuloma, syphilis sporotrichosis and bromide or iodine rash. The pathologic picture is similar to that of tuberculosis, with giant cells, except that the double-contoured bodies of blastomycosis are found in the tissue sections. The systemic type terminates fatally in 90 per cent of cases, and the

5. Henrici, A. T.: Molds, Yeast and Actinomycoses, New York, John Wiley & Sons, Inc., 1930.

6. Jacobson, H. P.: Fungous Diseases, Springfield, Ill., Charles C Thomas, Publisher, 1932.

7. Strong, R. P.: Stitt's Diagnosis, Prevention and Treatment of Tropical Diseases, Philadelphia, The Blakiston Company, 1942.

8. Stober, A. M.: Systemic Blastomycosis: A Report of Its Pathological, Bacteriological and Clinical Features, Arch. Int. Med. **13**:509 (April) 1914.

disease lasts from three weeks to three years. The treatment is symptomatic, together with rest, good food and administration of vitamins and potassium iodide.

Reports of fungous infection of the eye are relatively uncommon, especially intraocular infection. Blastomycosis of the eye has been reported in a few instances. Ball [9] illustrates a case of blastomycotic dermatitis involving the eyelids. In most cases of blastomycosis involving the eyes there has been a direct extension from the conjunctiva or the lids. In 1 such case, reported by Ferguson,[10] a tubercle-like growth on the conjunctiva developed from a beefy-looking growth on the cheek. McKee [11] reported a case of blastomycosis destroying the lids and producing ulcers of both corneas. It had also spread from the cheek and did not become intraocular. Wilson [12] described a case of conjunctival blastomycosis which developed from the scratch of a fowl. The antecedent history of injury followed a week later by the appearance of the lesion is a valuable point with respect to the incubation period.

Churchill and Stober [13] recovered a pure culture of blastomycetes from the vitreous of an eye of a patient who had systemic blastomycosis. A description of the ocular lesion was not given except that the eye was affected by the disease. Schwartz [14] gave the only pathologic report of an eye infected with blastomycosis that I have been able to find in the literature. In the autopsy report lesions of the skin, subcutaneous tissue, lungs, spleen, knee joint and eye are mentioned. The ophthalmic report was as follows:

> The cornea was . . . thickened and showed a perforation . . . near the limbus. . . . The anterior chamber and iris angle were almost entirely obliterated by an exudate of polymorphonuclear leukocytes, blastomycetes and giant cells. In the central portion of the iris was a medium sized area of necrosis. . . . The organisms were of variable sizes, having a highly refractile, double-contoured capsule, surrounding a granular or dark staining mass.

REPORT OF A CASE

W. M., a white man aged 64, a night watchman, was first admitted to the hospital in July 1942, with polyarthritis of six months' duration. The cutaneous

9. Ball, J. M.: Modern Ophthalmology, Philadelphia, F. A. Davis Company, 1927, p. 272.

10. Ferguson, A. S.: Blastomycoses of Eye and Face Secondary to Lung Infection, Brit. M. J. **1**:442 (March 17) 1928.

11. McKee, S. H.: Blastomycoses of the Cornea, Internat. Clin. **3**:50 (Sept.) 1926.

12. Wilson, R. P.: Blastomycoses of the Conjunctiva, Bull. Ophth. Soc. Egypt **28**:99, 1936.

13. Churchill, T., and Stober, A. M.: A Case of Systemic Blastomycoses, Arch. Int. Med. **13**:568 (April) 1914.

14. Schwartz, V. J.: Intraocular Blastomycoses, Arch. Ophth. **5**:581 (April) 1931.

lesions were of six weeks' standing, but the history was not accurate. The left elbow, left ankle and right knee joint were swollen and painful. He had a generalized papular disease of the skin, with some pustules covered with large scabs. The right pupil was sluggish and small. The temperature varied from 99 to 100 F. almost every afternoon but was normal in the morning. The urine showed a 1 plus reaction for albumin, a 1 plus reaction for pus and a rare hyaline cast. Examination of the blood revealed 3,800,000 red cells and 13,300 white cells per cubic millimeter, 70 per cent hemoglobin, 76 per cent polymorphonuclear leukocytes, 15 per cent lymphocytes, 2 per cent eosinophils and 7 per cent monocytes. His stay in the hospital was one week at this time.

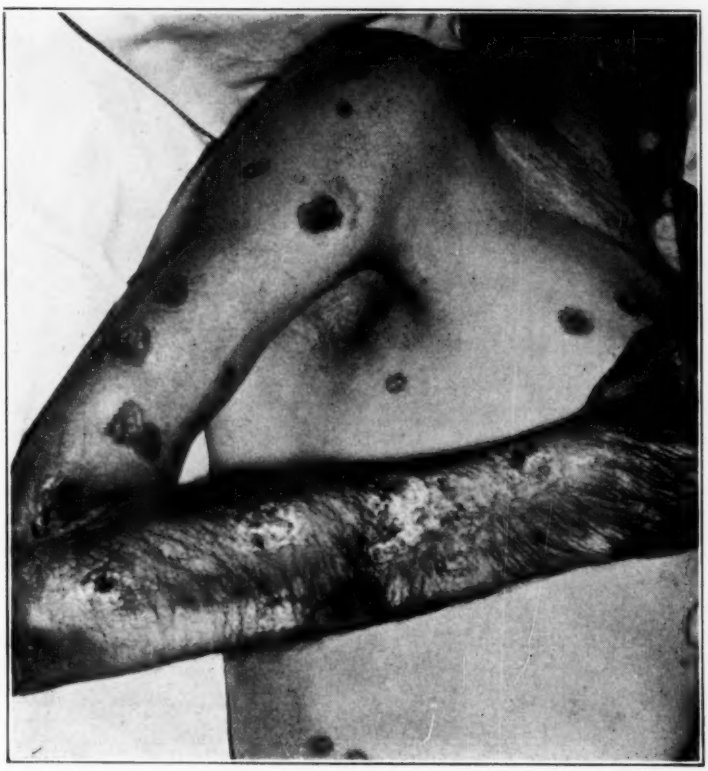

Fig. 1.—Discoid, discrete, scaly, elevated lesions of the skin of the right arm and forearm and the right side of the trunk.

He was readmitted to the hospital on Sept. 20, 1942, with severe pain in his right eye. He still had the skin disease and the polyarthritic symptoms; in addition, he was mentally confused, disoriented, emaciated and dehydrated. The cutaneous lesions were discoid and measured 0.5 to 2 cm. in diameter; they were distributed over the nose, cheeks, lobes of the ears, neck, hands, forearms, trunk, legs and ankles. Over the trunk the lesions were in various stages of evolution, healing with violaceous, atrophic scars (figs. 1 and 2). There were red, tender, swollen abscesses on the left elbow, the left ankle and the right

knee joint. The temperature, usually 99 to 100 F., occasionally reached 101 F. The urine showed a trace of albumin, and the pus cell content was graded 2 plus. The blood count revealed 5,000,000 red cells and 22,100 white cells per cubic millimeter, 77 per cent hemoglobin, 80 per cent polymorphonuclear leukocytes, 13 per cent lymphocytes and 7 per cent monocytes. The reaction to the Mazzini test was negative. A Mantoux test gave a negative reaction to tuberculin in 1:1,000 dilution. The spinal fluid was clear and colorless, with no cells. The total protein was 27 mg. per hundred cubic centimeters; the Kolmer reaction was negative and the colloidal gold curve was 1122200000. Biopsy of

Fig. 2.—Discrete, disk-shaped, pink lesions of the skin with scaly, elevated border. Some are covered with brown crusts.

the skin showed that the epidermis was the site of pronounced hyperplasia, confined more or less to the pigment cell layer. There were a superficial downgrowth of rete pegs and moderate edema of the squamous epithelium. Beneath the epithelium in the upper papillary portion of the corium was a heavy infiltration of polymorphonuclear leukocytes and epithelioid cells, all of which tissue was edematous. Scattered through this cellular infiltrate were numerous giant cells in which double, refractile, yeastlike bodies were seen. They were thought to be the so-called Blastomyces hominis, typical of blastomycosis of the skin.

A culture of material from the cutaneous lesions of blastomycosis yielded a growth of a fungus identified as Candida parapsilosis.

Roentgenograms of the right knee, tibia and fibula and the right side of the skull revealed irregular areas of destruction without reaction of the bone around the lesions. There was destruction of the lower third of the patella (fig. 3).

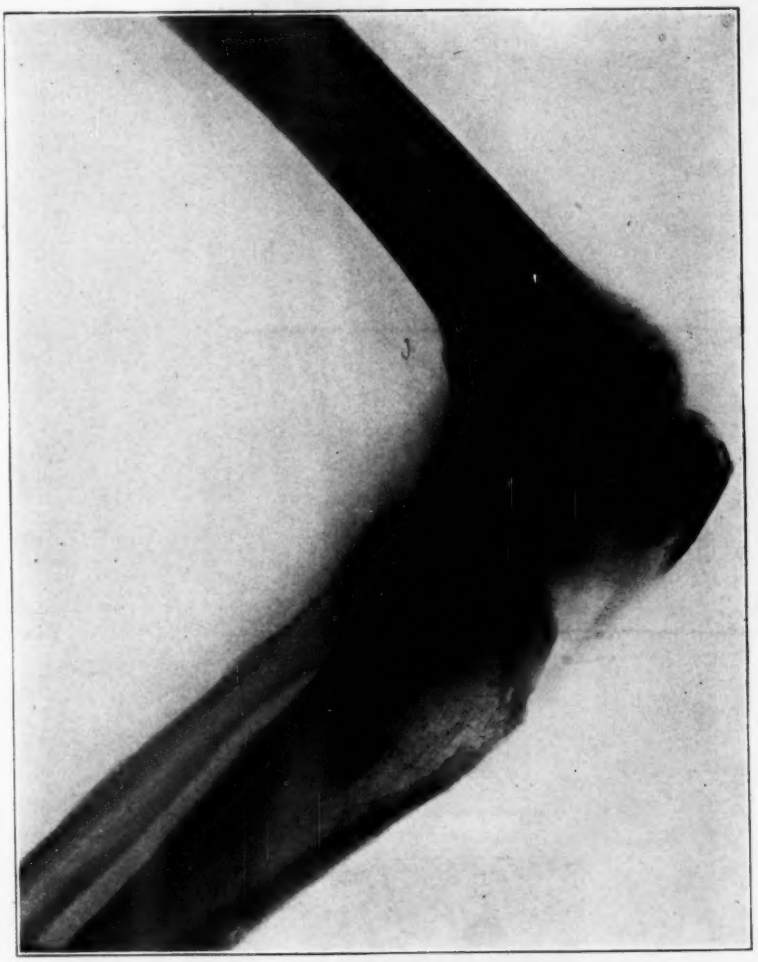

Fig. 3.—Roentgenogram of the right knee, showing irregular areas of destruction without reaction of the bone. The lower third of the patella is destroyed.

The tibial lesions (fig. 4) were mainly confined to the cortex in its middle and lower thirds. The lower end of the femur showed subcortical involvement. The skull had two areas of destruction in the right parietal bone. Irregular scattered areas of consolidation in both lungs, with linear bands extending outward from the hilus, were seen in the roentgenogram of the chest. It was the conclusion of the roentgenologist that the appearance and location of the lesions in the bone, together with the type of lesion in the lungs, favored a diagnosis of blastomycosis.

Fig. 4.—Cortical lesions of the tibia in its middle third.

Fig. 5.—Injection of the ciliary body of the right eye. The pupil was small and fixed, with posterior synechias. A yellow nodule occurred at the free border of the iris, and a yellow growth extended into the angle of the chamber from 4 to 6 o'clock.

Fig. 6.—Section representing 1.4 mm. of lung. Double-contoured, yeastlike blastomycetes occur in the cytoplasm of the endothelial cells.

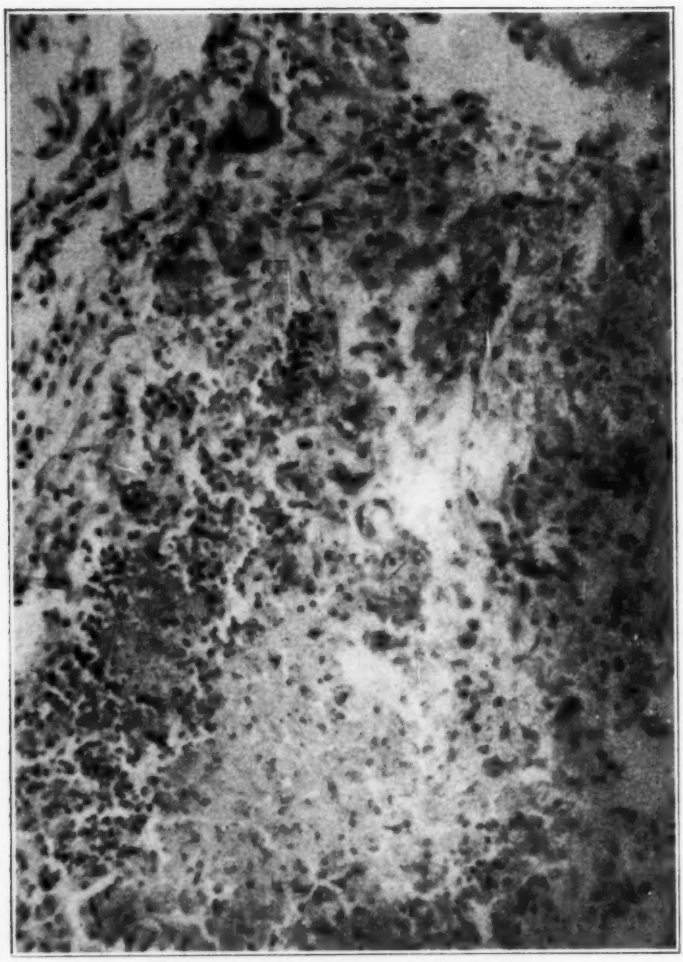

Fig. 7.—Section representing 25 mm. of the prostate gland, showing the granulomatous type of necrosis.

Fig. 8.—Section of the prostate gland seen with the oil immersion lens. Double-contoured bodies of the yeast cell are shown.

The patient had severe photophobia, moderate injection of the ciliary body of the right eye, a total posterior synechia and a small, fixed pupil. At 8 o'clock on the free margin of the iris was a yellowish, tubercle-like nodule. Extending into the angle of the anterior chamber at the limbus was another yellow, tubercle-like lesions, apparently protruding through the iris at its base (fig. 5). Paracentesis of the anterior chamber and examination of the aqueous for blastomycetes gave negative results, but the plasmoid intraocular fluid was not aspirated.

The patient's condition continued to have a downhill course, and he died on Dec. 7, 1942.

Autopsy.—The conspicuous lesions on postmortem examination were multiple nodular areas scattered throughout both lungs. Microscopic examination of these

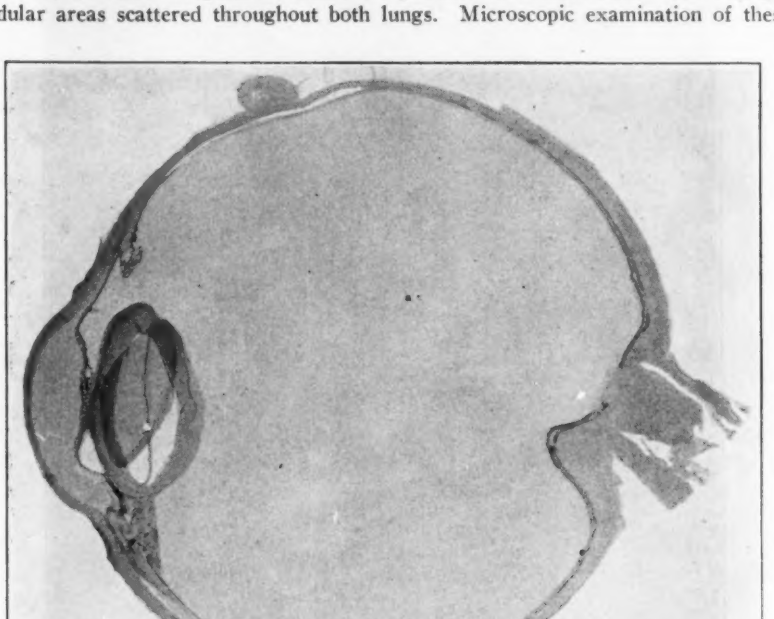

Fig. 9.—Inflammatory mass involving the root of the iris and the ciliary processes, occluding the infiltration angle and forming an adhesion to the lens. United States Army Medical Museum negative 77205.

foci revealed that the alveoli were filled with endothelial leukocytes and a few polymorphonuclear leukocytes. The lesion was of proliferative character, and many of the endothelial leukocytes contained double-contoured yeast cells (fig. 6).

The kidneys weighed 125 Gm. each, and scattered throughout the cortex were multiple pinhead-sized, greenish nodules. On microscopic examination these were found to be multiple abscesses containing yeast buds.

The prostate gland was moderately enlarged, and scattered over the cut surfaces were multiple pinpoint areas of necrosis, from which there could be expressed a thick, greenish exudate. Microscopic study of sections from these areas revealed multiple abscesses (fig. 7) with proliferation of cells, and in the

abscesses were many yeastlike cells, some of them surrounded by double-contour disks and others containing small buds (fig. 8).

Exploration of the right patella revealed necrotic areas filled with greenish exudate, and in these areas yeast cells were also found on microscopic study. A few areas of osteoporosis were observed at the vertex of the skull, and the brain was entirely normal.

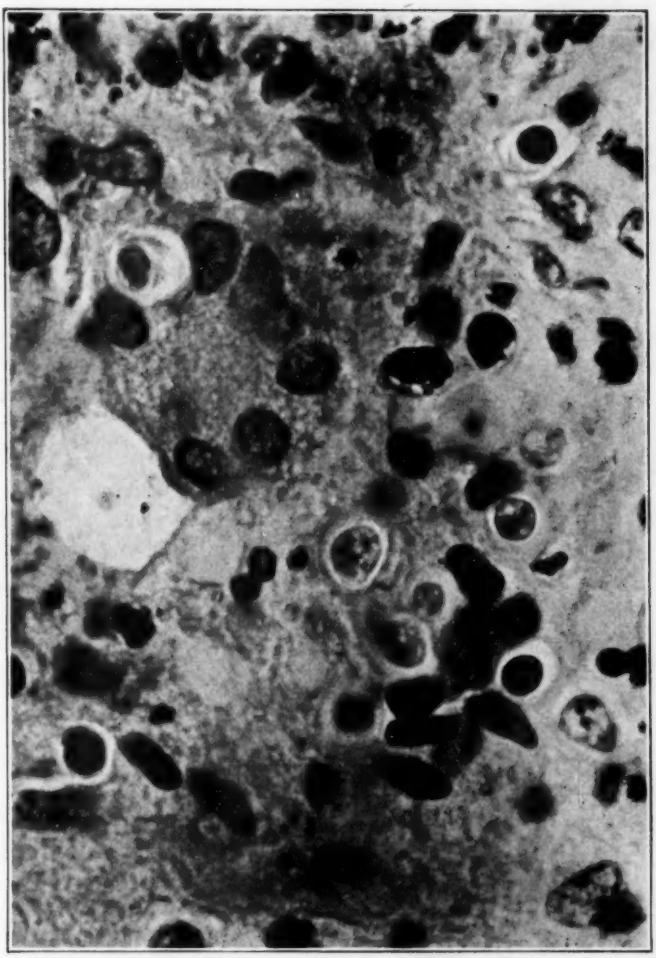

Fig. 10.—Giant cell of the blastomycotic inflammatory reaction of the iris, showing budding and double-contoured yeast cells. United States Army Medical Museum negative 77205.

Examination of the Eye.—The eye was enucleated and submitted to the American Registry of Pathology of the Army Medical Museum for study. Report of the examination follows.

"The specimen consisted of a partially collapsed eye, measuring 24 by 24 by 24.5 mm. The pupil was small. The eye was opened between the horizontal

and the vertical plane. A dense, opaque lesion involved the ciliary body and the filtration angle on one side (fig. 9). There were retinal folds around the optic disk. The vitreous was cloudy. The iris was bound down to the swollen lens.

"Clumps of polymorphonuclear leukocytes and large mononuclear wandering cells and lymphocytes clung to the posterior surface of the cornea. A small amount of serous exudate was present in the anterior chamber. There were exten-

Fig. 11.—Inflammatory process at the root of the iris; capsular cataract.

sive posterior synechias and, one one side, an early anterior synechia. The iris was atrophic and diffusely infiltrated with plasma cells and lymphocytes, and an inflammatory pupillary membrane adhered to the anterior capsule of the lens. On one side a mass of inflammatory tissue involved the root of the iris and the ciliary processes and occluded the filtration angle and formed an adhesion to the lens. Tubercles were seen in the deep corneal lamellas and around the canal

of Schlemm. In the lesion were small abscesses, areas of necrosis, lymphocytes, plasma cells, epithelioid cells and giant cells. Throughout the mass and, in great numbers, in the giant cells (fig. 10) were double-contoured bodies, among which budding forms were found. Beneath the inflammatory mass was a capsular cataract (fig. 11). Lens fibers had undergone morgagnian degeneration. There was serous exudate beneath the detached ciliary body. Colloid excrescences were present on Bruch's membrane. There were degenerative changes in the retinal layer of rods and cones and small subretinal serous exudates. The lamina cribrosa was depressed.

"The diagnosis was blastomycotic iridocyclitis, cataract and secondary glaucoma."

Anatomic Diagnosis.—The anatomic diagnosis was blastomycosis involving the skin, lungs, prostate gland, kidneys, bone and eye.

SUMMARY

A review of the literature and the study of a case of endogenous blastomycosis (Gilchrist's disease) are presented. Considering the widespread distribution of this disease throughout the body, it would not be unusual to find intraocular changes. From this case, and from other cases reported in the ophthalmic literature, one would conclude that metastatic uveitis associated with systemic blastomycosis is not so rare as has generally been thought. If the eye is implicated during the course of a fungous infection, I suggest the withdrawal of the plasmoid intraocular fluid for cytologic examination and culture. As a part of the postmortem examination, the histopathologic study of the ocular structures may prove helpful in demonstrating the protean manifestations of this disease.

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ACID BURNS OF THE EYE

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AND
H. HERRMANN, M.D.
BALTIMORE

THE more benign character of acid burns of the eye was first contrasted with that of alkali burns by George Joseph Beer in 1813, who stated that "the effect of mineral acids of equal saturation is rarely so destructive for the cornea as is slaked lime." Since then there have been numerous clinical reports of ocular injury by many types of acid.[1] The patients whose cases have been reported received

From the Wilmer Ophthalmological Institute of the Johns Hopkins University and Hospital.

1. (*a*) Rochat, G. F.: Schädigung der Hornhaut durch Schwefelwasserstoff, Klin. Monatsbl. f. Augenh. **70**:152-154, 1923; abstracted, Zentralbl. f. d. ges. Ophth. **10**:196, 1923. (*b*) Hensen, H.: Ueber einen Fall von Hornhauttransplantation nach Verätzung nebst Mitteilung über Beseitigung von Pseudopterygium der Hornhaut durch Thiersche Läppchen, Klin. Monatsbl. f. Augenh. **72**: 172-175, 1924; abstracted, Zentralbl. f. d. ges. Ophth. **13**:80, 1925. (*c*) Loree, M. C.: Automobile Battery Burns of the Eyes and Adnexa with Case Reports, J. Michigan M. Soc. **23**:292-294, 1924; abstracted, Zentralbl. f. d. ges. Ophth. **14**:665, 1924-1925. (*d*) Stocker, F.: Praktische Bemerkungen zur Pathologie und Therapie der Schwefelwasserstofferkrankung der Augen. Med. Klin. **1**:167-168, 1931; abstracted, Zentralbl. f. d. ges. Ophth. **25**:298, 1931. (*e*) Becker: Lippenschleimhaut-Frühplastik bei Limbusnekrose nach Schwefelsäureverätzung, Klin. Monatsbl. f. Augenh. **86**:384-385, 1931; abstracted, Zentralbl. f. d. ges. Ophth. **25**:340, 1931. (*f*) Oshima, T.: Zwei Fälle von Verätzung der Augen, des Gesichts, des Nackens und der Schultern durch Schwefelsaure, Acta Soc. ophth. jap. **35**:295-296, 1931; abstracted, Zentralbl. f. d. ges. Ophth. **25**:485, 1931. (*g*) d'Osvaldo, E.: Caustieazioni da anidride acetica, abstracted, ibid. **26**:656, 1932. (*h*) Kaminskij, D.: Fall von beiderseitiger Verätzung der Augen mit Essigsäure, Sovet. vestnik oftal. **3**:378-380, 1933; abstracted, Zentralbl. f. d. ges. Ophth. **31**:437, 1934. (*i*) Coppez, J. H., and Brenta: Brûlures oculaires par l'acide sulfurique, Bull. Soc. belge d'opht. **72**:88-100, 1936; abstracted, Zentralbl. f. d. ges. Ophth. **37**:432, 1937. (*j*) Berezinskaya, D.: Augenverätzungen mit Säuren und Alkalien, Sovet. vestnik oftal. **8**:319-332, 1936; abstracted, Zentralbl. f. d. ges. Ophth. **37**:44, 1937. (*k*) Hisatomi, Y.: Ein seltener Fall von Augenverätzund durch Formalinlosung, Chuo-Ganka-Iho **31**:22-29, 1939; abstracted, Zentralbl. f. d. ges. Ophth. **44**:671, 1939-1940. (*l*) Pollet-Delille, F.: Caractères des brûlures accidentelles de l'oeil par l'acide chromique, Bull. Soc. franç. d'opht. **52**:221-225, 1939; abstracted, Zentralbl. f. d. ges. Ophth. **45**:417, 1940.

burns of varying degrees of severity. Those with mild burns recovered uneventfully regardless of the type of treatment, whereas those exposed to high concentrations of acid usually had permanent corneal opacification, perforation of the globe or extensive symblepharon. Since it is impossible to determine the exact degree of exposure from a history of the accident, several investigators [2] have determined the tolerance of the rabbit eye for a few drops of various concentrations of different acids. These experiments have not yielded accurate quantitative data concerning the lowest p_H which the normal cornea will tolerate without injury, nor have they considered the penetrating power of the acid or the importance of the anion used.

In an introductory study of these problems, Friedenwald, Hughes and Herrmann [3] presented an outline of the methods used for the quantitative estimation of the acid-base tolerance of the rabbit cornea as follows: 1. Isotonic solutions which had a known p_H and, when possible, were well buffered, were used. 2. Both the intact cornea and the cornea denuded of epithelium were irrigated for ten minutes with a standard amount of the test solutions, and 0.1 cc. of the same solutions were injected intracorneally in other eyes. 3. A numerical estimation of the severity of several characteristic ocular symptoms produced by the acids was used to obtain a grade which could be manipulated statistically and graphically. With these technics, results were obtained which were reproducible with a high degree of uniformity. It was found that the corneal epithelium had a highly protective effect against the penetration and damaging effects of acid. In addition, the corneal stroma itself was found to have some buffering capacity for solutions below p_H 4.0. However, ocular lesions were produced by exposure to isotonic solutions of hydrochloric acid of 0.005 normal concentration (p_H 2.5) or stronger or by exposure to isotonic solutions of citrate-phosphate-borate buffer at p_H 4.5 or below.

IMPORTANCE OF THE ANION

A plausible explanation of the discrepancy in the p_H levels at which lesions are produced by hydrochloric acid and the buffer solution is

(*m*) Winkler, A.: Phenolverätzung beider Augen und Allgemeinfolgen nebst einingen Bemerkungen über die Therapie von Augenverätzungen, Klin. Monatsbl. f. Augenh. **102**:810-815, 1939.

2. Siegrist, A.: Konzentrierte Alkali und Säurewirkung auf das Auge, Ztschr. f. Augenh. **43**:176-194, 1920; abstracted, Zentralbl. f. d. ges. Ophth. **3**:220, 1920. Yoshimoto, R.: Ueber experimentelle Säure- und Laugenverätzungen der Augen, Arch. f. Augenh. **99**:188-206, 1928. d'Osvaldo.[1g] Kaplan, J. D.: Erste Hilfe bei chemischen Verbrennungen der Augen, abstracted, Zentralbl. f. d. ges. Ophth. **36**: 391, 1936. Berezinskaya.[1j]

3. Friedenwald, J. S.; Hughes, W. F., Jr., and Herrmann, H.: Acid-Base Tolerance of the Cornea, Arch. Ophth. **31**:279 (April) 1944.

to be found in the greater protein affinity of the trivalent anions of the buffer than of the chloride ion. Such an explanation would relate the tissue damage done by caustic acid solutions to the precipitation and denaturation of protein which these produce. In the present study we have put this hypothesis to direct test by comparing the effect on the cornea of various acid ions which are known to differ in their protein affinities. If the corneal damage depends on precipitation and denaturation of protein, then the anions with greater protein affinity should produce lesions at higher p_H than the anions of lesser protein affinity, but the clinical and pathologic character of the lesions resulting from these various anions should be essentially the same. This is precisely the result shown by the experiments which we are now reporting.

The following acids, arranged in order of their increasing protein affinity and protein-precipitating ability, were used: hydrochloric, trichloroacetic, metaphosphoric, sulfosalicylic, picric, tungstic and tannic. Clinical reactions produced by solutions of these acids on the rabbit cornea were studied over a p_H range of 1 to 9. The solutions of the acids were brought to the desired p_H by addition of sodium hydroxide. In order to control the stability of the p_H and overcome the slight buffering capacity of the cornea itself, the acid solutions were buffered by addition of isotonic citrate-phosphate-borate solutions of the same p_H. Both buffered and unbuffered solutions were tested on rabbit cornea. The effect of the buffer solution alone was also tested.

The results of the experiments are shown in figure 1. The maximum lesions produced by these anions were similar in clinical appearance and in histologic characteristics. Except for their uniformity, these histologic and clinical observations have little bearing on the present argument and are therefore presented in subsequent sections. Corneal lesions were produced by chloride and trichloroacetate solutions (without added buffer) only up to p_H 3.0. The buffer solutions alone produced lesions up to p_H 4.5. Metaphosphate and sulfosalicylate solutions (with and without added buffer) produced lesions up to p_H 5.5 to 6.0. Picrate, tungstate and tannate solutions (with and without added buffer) produced lesions up to p_H 9.

The reaction produced by hydrochloric acid occurred at a somewhat higher p_H than was to have been expected by comparing its protein-precipitating power with that of the other agents used. However, accurate data on the protein-denaturing effect of these solutions are not available, and our observations do not suffice to explain this small discrepancy.

Except for this irregularity with respect to hydrochloric acid, our experiments indicate that the anions with greater affinity for proteins produce corneal lesions at a higher p_H than the anions with lesser

protein affinity but that the maximum lesion produced by any one of these agents is essentially the same. Consequently, we may relate the clinical reactions to the formation of protein-anion combinations. Since the tissue damage is not reversed by return of the p_H to neutrality, it follows that the corneal proteins have been irreversibly changed, i. e., denatured by the process.

The possible role of penetrating power in relation to the severity of the lesions produced was tested by comparing the reaction to intracorneal injection with that to irrigation after removal of the corneal epithelium, using the same solutions. It was found that all the anions tested except the chloride ion produced somewhat more severe reac-

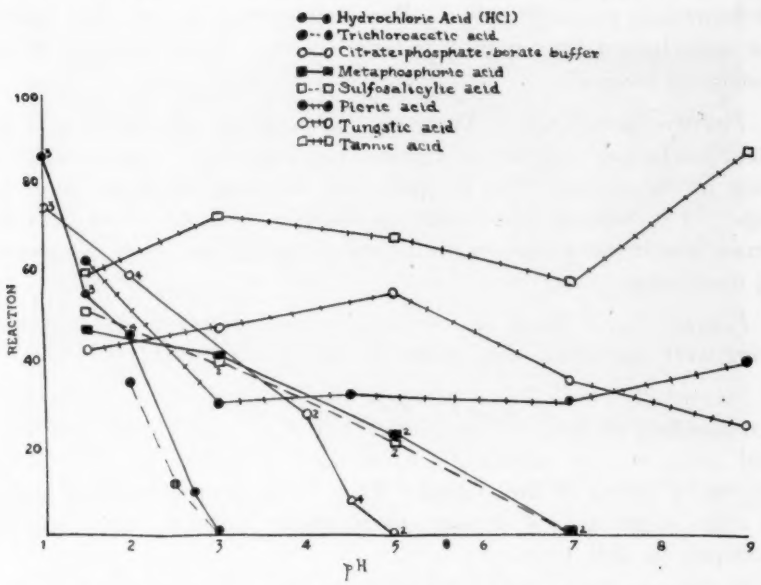

Fig. 1.—Severity of the reactions produced in the rabbit cornea by the intracorneal injection of several acids of varying p_H, showing that anions with high protein affinity and protein-precipitating ability produce lesions at a higher p_H than anions with lesser protein affinity.

tions on injection than on irrigation. If the corneal epithelium was not removed, the severity of the corneal lesions after irrigation was, of course, much less.

CLINICAL CHARACTERISTICS OF ACID BURNS OF THE RABBIT CORNEA

Corneal opacification begins within a few seconds after the irrigation is started if the acid solution is concentrated (e. g., tenth-normal hydrochloric acid) or if the anion has a high protein affinity and protein-precipitating ability (e. g., trichloroacetic, sulfosalicylic or tannic acid). Severe corneal burns with various acids follow a similar clinical course.

The sequence of events will therefore be described for a burn produced in a rabbit eye by irrigation for ten minutes with tenth-normal solution of hydrochloric acid made isotonic with sodium chloride.

During Irrigation.—A lacy network of fine punctate opacities appeared in the exposed area of the cornea, gradually coalescing into a smooth, dense opacification, through which the outlines of the pupil could hardly be seen. There was a sharp line of demarcation between the area immediately in contact with the irrigating fluid and that portion of the cornea which was loosely covered by the lids or the nictitating membrane. During the early stages of irrigation the corneal epithelium took a punctate green stain with fluorescein. However, later, the fluorescein produced only a yellow stain over the dense white opacity. The epithelium did not peel off in large sheets. The conjunctiva became moderately ischemic.

Twenty-Four Hours.—There was a moderate amount of mucopurulent discharge, conjunctival redness and chemosis. Edematous thickening of the cornea could be made out with the hand slit lamp and loupe. The burned area remained sharply delimited from the clear cornea, which was protected during irrigation by the lids of the nictitating membrane.

Fourth Day.—Much of the conjunctival reaction had subsided. There were ordinarily many dilated vessels at the limbus.

Seventh to Tenth Day.—Many of the limbal blood vessels could be seen invading all layers of the cornea, either as large trunks and superficial loops or, less commonly, as straight, brushlike projections into the deeper layers of the cornea. They most often proceeded around the edges of the area of densest opacification. Corneal edema was well developed by this time.

Fourteenth Day.—Most of the eyes showed gross ulceration of the cornea, with perforation resulting in about one-half the severely burned eyes. This usually led to phthisis bulbi, although some perforations were repaired with an exuberant growth of fibrous and granulation tissue. If perforation did not occur, regression of the vascularization and corneal edema began, the corneal vessels becoming bloodless in two or three weeks. In less severely burned eyes the cornea might become clear except for a relatively thin, but permanent, "silky" opacity. Symblepharon was not noted in any of the rabbits.

PATHOLOGIC CHARACTERISTICS OF ACID BURNS OF THE EYE

Rabbit eyes were irritated for ten minutes with a tenth-normal solution of hydrochloric acid made isotonic with sodium chloride, followed by brief irrigation with isotonic solution of sodium chloride. Specimens

were obtained immediately after the irrigation was stopped and forty-five minutes, two hours, eight hours, twenty-four hours, seven days and twenty-one days later. These were fixed in Zenker solution for twenty-four hours, washed for twenty-four hours and then dehydrated in alcohol. Hemotoxylin and eosin, Mallory's connective tissue strain and toluidine blue for metachromatic staining were employed (see figures).

Immediately After Irrigation.—The cytoplasm of the corneal epithelium gave acidophilic staining reactions, and the superficial cells were desquamated.

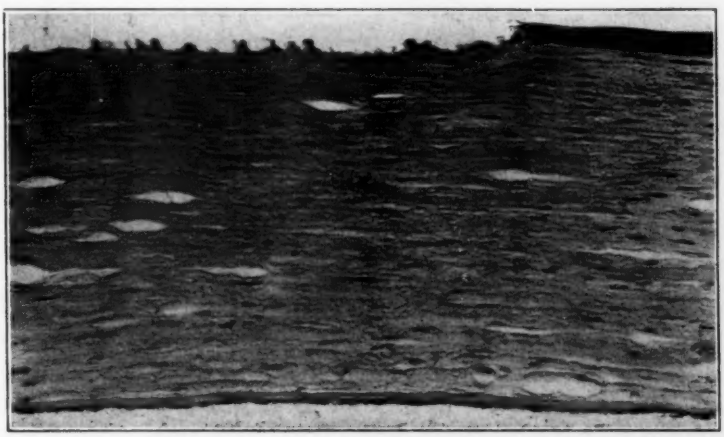

Fig. 2.—Section of cornea taken forty-five minutes after irrigation with tenth-normal hydrochloric acid for ten minutes. The sharp boundary of the lesion is well seen in the epithelium. The endothelium remains intact. × 100.

Forty-Five Minutes (fig. 2).—Coagulated proteins appeared in the anterior chamber.

Two Hours.—Albuminous material appeared under the corneal epithelium, and the corneal stroma was mildly edematous.

Four Hours.—The corneal epithelium was greatly altered, and acidophilic granules appeared in the cytoplasm. There were some edema and fraying of the cells in the substantia propria, but the corneal endothelium appeared essentially normal.

Eight Hours.—Sections (figs. 3 and 4) demonstrated a sharp transition between the normal corneal epithelium and the burned epithelium, with acidophilic cytoplasm, pyknosis of the nuclei and general shrinking of the epithelial layer. With Mallory's connective tissue stain, the epithelium was a deep maroon instead of a normal light red-

dish purple. The stroma was edematous, and there were some obvious shrinking and disappearance of the cell nuclei.

Twenty-Four Hours (fig. 5).—Polymorphonuclear cells were found at the limbus entering the superficial layers of the stroma. Metachromatic staining with toluidine blue showed no appreciable loss of mucoid.

Seven Days (fig. 6).—The corneal epithelium had regenerated over most of the burned area. It was irregular, thin, degenerated and detached from the central portion of the stroma. Blood vessels were found at the limbus in the anterior half of the corneal stroma. The stroma itself

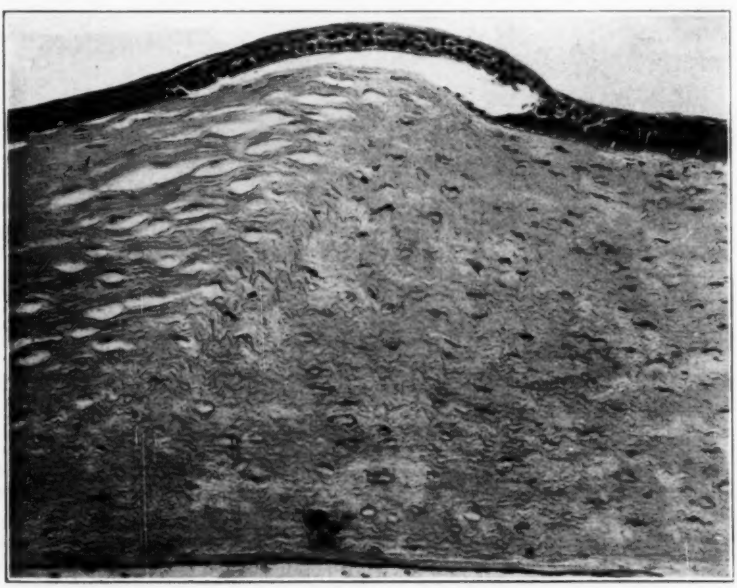

Fig. 3.—Section of cornea taken eight hours after irrigation with tenth-normal hydrochloric acid. A slanting line of sharp contrast appears between the burned (left) and the normal (right) area. Although the epithelium is thin and necrotic, there is no complete desquamation. The texture of the stroma is altered, with loss of stromal cells. × 100.

was edematous (fig. 7). The endothelium had proliferated in places forming a layer several cells deep. Metachromatic staining now showed almost complete loss of mucoid.

Two to Three Weeks.—An area of corneal ulceration was being repaired by proliferation of fibrous tissue and blood vessels, the crater of the ulcer being filled with inflammatory cells.

In contrast to burns with alkalis and indelible dyes, the special characteristics of acid burns may be enumerated as follows: (1) some-

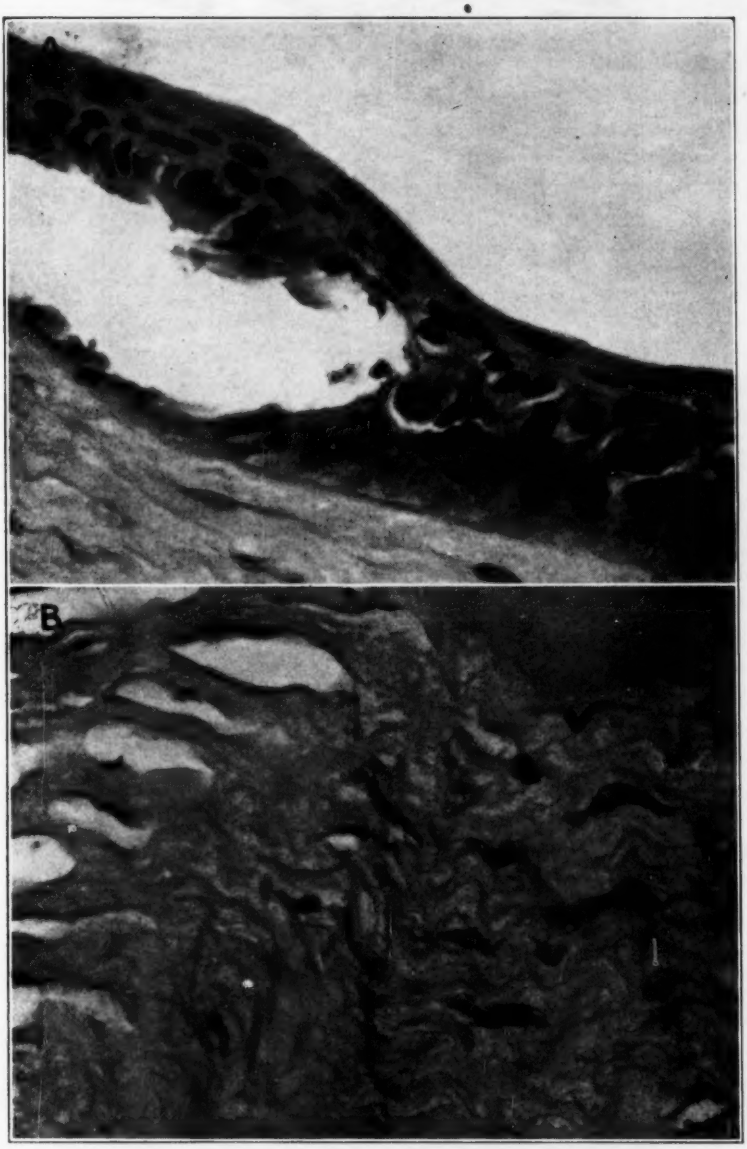

Fig. 4.—Sections of cornea taken eight hours after irrigation with tenth-normal hydrochloric acid. *A* shows the pronounced pyknosis of nuclei in the basal layers of the involved epithelium. The cytoplasm is diminished and is more acidophilic. × 500. *B* shows the contrast between normal stroma, on the right, and burned stroma, on the left. There are pronounced pyknosis and loss of nuclei in the involved area. Changes in the collagen fibers begin to be apparent. × 500.

Fig. 5.—Section of cornea taken twenty-four hours after irrigation with tenth-normal hydrochloric acid, showing the infiltration of polymorphonuclear leukocytes in the anterior layers of the cornea near the limbus. × 500.

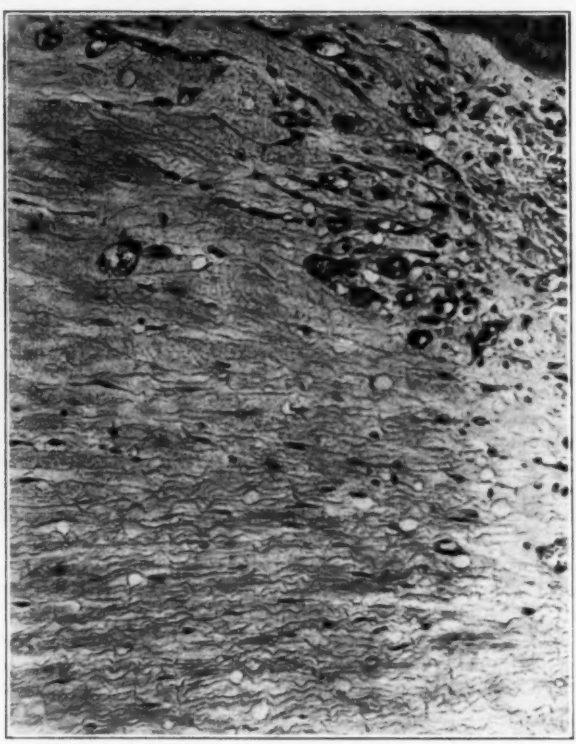

Fig. 6.—Section of cornea taken seven days after irrigation with tenth-normal hydrochloric acid, showing the vascularization in the anterior layers of the stroma extending in from the limbal vessels. × 200.

what slower penetration into the eye, with rather sharp demarcation of the lesion; (2) a clinical course which can be prognosticated with some accuracy within a few hours after the injury (i. e., a lesion of nonprogressive type); (3) little tendency of the corneal epithelium to desquamate; (4) little tendency to exudative manifestations, such as purulent discharge with or without secondary infection, intense leukocytic infiltrations of the conjunctiva, cornea and iris, or fibrinous iritis; (5) little evidence of selective involvement of the blood vessels, e. g., productions of intense early edema or petechial hemorrhages in the

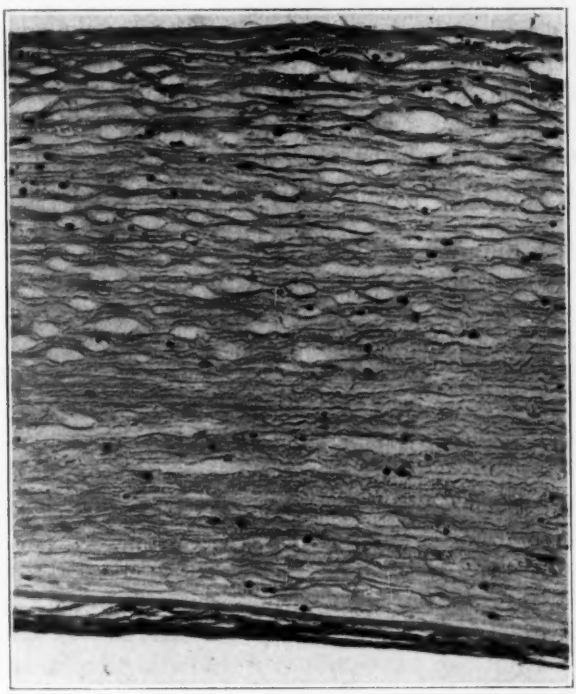

Fig. 7.—Section of cornea taken seven days after irrigation with tenth-normal hydrochloric acid, showing edema of the stroma, diffuse infiltration with polymorphonuclear leukocytes and reduplication of the endothelium. The epithelium is irregular and is not adherent to the stroma but is not completely desquamated. × 100.

conjunctiva or, later, of ischemia and thrombosis of the vessels around the limbus and in the iris; (6) marked tendency of the relatively opaque cornea to heal, and (7) no early loss of corneal mucoid (see next section).

EFFECT OF ACID ON CORNEAL MUCOID

Estimations of corneal mucoid were made by two methods: (1) metachromatic staining with toluidine blue (1:1,000), and (2) determina-

tions of the hexosamine content of the cornea, by Dr. Karl Meyer and Dr. Eleanor Chaffee.[4] In contrast to alkali-burned corneas, corneas exposed to irrigation with tenth-normal hydrochloric acid for ten minutes showed no early loss of metachromatic staining or hexosamine content. However, after one week, metachromatic staining disappeared in the scarred areas, and the hexosamine content was reduced.

CONCLUSIONS

Acid burns of the eye are essentially nonprogressive, and late relapses are uncommon. The severity of the corneal lesion produced by acids is directly related to the protein affinity of the anion. Anions with high protein affinity and protein-precipitating ability produce corneal lesions at a higher p_H than anions with low protein affinity, but these large anions (with high protein-precipitating ability) show poor penetration through the corneal epithelium and poor diffusibility in the stroma. It is suggested that the clinical and pathologic characteristics of acid burns of the cornea may be explained by such precipitation and denaturation of the proteins of the cornea.

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4. Drs. Meyer and Chaffee, of Columbia University, determined the hexosamine content of acid-burned rabbit corneas and have permitted us to include the conclusions from their studies in the present report.

TESTS FOR DETECTION AND ANALYSIS OF COLOR BLINDNESS

II. Comparison of Editions of the Ishihara Test

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AND
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IN an earlier report on the Ishihara test for color blindness [1] we presented a brief history of the test from the original edition, issued in 1917, to the last Japanese edition of which we have a record in this country, the ninth edition, issued in 1940. Mention was also made of the British reprint of the ninth edition, issued in London in 1943.

That report is the first of a series designed to evaluate in turn various color tests as means of analyzing and detecting defective color vision. The data reported were collected during the course of a study of some 106 persons having defective color vision of varying types and amounts, including 74 who had definite defects in color vision and 32 who had low, but normal, color vision. To study these persons a comprehensive battery of color tests was used; some of these are well known in the field of color blindness testing, some are less well known and some were devised in this laboratory. The fifth edition of the Ishihara test, one of the best known of the shorter editions, was selected for inclusion in the battery of tests. The results obtained from the entire battery aided in the classification of the defect in color vision as to type and extent and at the same time permitted us to evaluate each test of the battery both as a diagnostic or screening medium (the purpose of which is to screen out the subjects with defective color vision from those with normal color vision) and as a medium for classification (the purpose of which is to determine the type and extent of the defect).

Concerning the fifth edition of the Ishihara test, it was concluded that when properly administered the test affords a good rough device for screening persons with defective red-green vision from persons with normal color vision if a performance score of 60 is taken as the

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1. Hardy, L. H.; Rand, G., and Rittler, M. C.: Tests for Detection and Analysis of Color Blindness: I. An Evaluation of the Ishihara Test, Arch. Ophth. **34**:295 (Oct.) 1945.

critical score, that is, if 60 per cent of the plates are read correctly. In the group tested no subject with defective color vision scored more than 58 and no subject with normal color vision less than 75. The Ishihara test is, however, only a gross test for defective red-green vision. It fails to classify the type of defective color vision (protanopia, protanomaly, deuteranopia, deuteranomaly, tritanopia, tritanomaly [2]) and cannot be used to give a satisfactory evaluation of the extent of the defect, no matter how carefully administered.

Because the different editions of the test have undergone significant changes not only in the number of plates but in other important aspects, we undertook a comparative study of the responses given and the scores obtained on several representative editions by a small group of persons with defective color vision. Typical of the other changes in the later editions is a variation, whether intentional or not, in the hue, value and chroma (that is, in the color, brightness and saturation) of the disks forming both digit and background; and in some instances in the general brightness relation between digit and background, in the massing of color in digit and background and in the number of plates bearing a two digit pattern.

This comparative study was made with the fifth and seventh Japanese editions; the British reprint of the ninth Japanese edition, which we shall call simply the ninth edition, and the Ishihara plates included in the American Optical Company's compilation of pseudoisochromatic plates. Only the plates intended for testing color-blind literate subjects were used, of which there are 12 in the fifth edition, 24 in the seventh and ninth editions and 10 in the American Optical Company's test. These plates consist of six series: Series 1 and 2 are of the "transformation pattern" type, in which the subject with defective color vision sees a different pattern than the subjects with normal color vision sees; series 3 and 4 are of the "vanishing digit" type, in which the pattern is not seen at all by the subject with defective color vision; series 5 contains a "hidden digit," which is supposedly seen only by the subject with defective color vision, and series 6 is the "diagnostic" type, intended for classification as to deuteranopia and protanopia. A fuller description of the six series of plates is given in the former report.[1] In the fifth edition there are 2 plates in each series; in the seventh and ninth editions, 4 plates in each series, and in the American Optical Company's test, 4 plates in series 1, 4 plates in series 2 and 2 plates in series 5.

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2. For a simple explanation of these terms, see the preceding article in this series [1] (page 298, footnote 14); also, Hardy, L. H., and Rand, G.: Recent Developments in Color Vision Testing, Graduate Lecture, Continuous Course no. 6 and 7, American Academy of Ophthalmology, 1944.

Twenty-two subjects with defective color vision to whom the entire battery of tests had been administered were available for the present work—7 deuteranomalous and 5 protanomalous subjects (anomalous trichromats) and 5 deuteranopes and 5 protanopes (dichromats). The testing distance was about 30 inches (76 cm.). A close approximation to I. C. I. Illuminant C was used throughout the work. The illumination on the test material was about 25 foot candles.

The general conclusion to be drawn from the study is that on the whole the three editions of the Ishihara test yield the same type of result, in spite of the changes that have been made in the number of plates and in the plates themselves, some of which are improved in one edition as compared with the others and others are less effective. The seventh and ninth editions have been improved over the fifth edition so far as trapping the protanomalous and protanopic types of subject is concerned; but the plates used for the classification of the type of red-green defective vision among the anomalous trichromats are less successful, particularly as reproduced in the seventh edition. None of the editions yields a differential score as to the extent of the defect in color vision. It seems probable from the data that the critical performance score of 60, marking the division between low normal and defective color vision, holds for the seventh and ninth editions of the test. This critical score, it will be remembered, was established for the fifth edition with the larger group of subjects, which included both observers with defective color vision and observers with low normal color vision. The Ishihara plates appearing in the American Optical Company's test are, however, for the most part poor selections and poor reproductions of the original Japanese plates and have less value for screening deuteranomalous and deuteranopic subjects than have the plates as reproduced by Ishihara.

The results are summarized in detail in tables 1 to 3. They will be discussed under three headings: (1) analysis of results obtained on the individual plates, (2) significance of performance scores on the entire test and (3) classification as to deuteranopia and protanopia, and deuteranomaly and protanomaly.

ANALYSIS OF RESULTS OBTAINED ON INDIVIDUAL PLATES

In table 1 is shown for each type of defective color vision the percentage of subjects who pass the individual plates of each edition under consideration, the plates being designated by both series number and plate number as they appear in the edition under consideration. The first 4 horizontal rows of figures under each edition show these percentages for each type of defective color vision and demonstrate the value of the individual plates for detecting each type. The bottom

TABLE 1.—*Analysis of Results Obtained on Individual Plates of the Ishihara Test, Editions 5, 7 and 9 (British reprint), and the Ishihara Plates in American Optical Company's Test* *

Type of Defective Color Vision	Number of Subjects	Percentage of Subjects with Each Type of Defective Color Vision Passing Individual Plates																							
		Series No. 1				Series No. 2				Series No. 3				Series No. 4				Series No. 5				Series No. 6			
		5th Edition (12 Plates) Plate No.																							
		2	3			4			5	6	7			8	9			10	11			12	13		
Anomalous Trichromasy																									
Deuteranomaly	7	57	72			0			0	0	14			14	29			14	0			14	29		
Protanomaly	5	80	100			0			0	0	0			0	0			0	0			20	20		
Dichromasy																									
Deuteranopia	5	0	0			0			0	0	0			0	0			0	0			0	0		
Protanopia	5	60	60			0			0	0	0			0	0			20	20			0	0		
All types of defective color vision	22	50	59			0			0	0	5			5	9			9	5			9	14		
		7th Edition (24 Plates) Plate No.																							
		2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
Anomalous Trichromasy																									
Deuteranomaly	7	43	14	0	14	0	0	0	0	14	14	0	0	29	29	0	0	43	29	14	0	43	57	43	43
Protanomaly	5	0	20	0	0	0	0	0	0	0	0	0	0	0	20	0	0	0	0	0	0	40	60	40	20
Dichromasy																									
Deuteranopia	5	0	0	20	0	0	0	0	0	0	0	0	0	20	0	0	0	20	0	0	0	0	0	0	0
Protanopia	5	0	20	0	0	0	0	0	0	0	0	0	0	0	20	0	0	0	20	20	20	0	0	0	0
All types of defective color vision	22	14	14	5	5	0	0	0	0	5	5	0	0	14	18	0	0	18	14	9	5	23	32	23	18
		9th Edition, British Reprint, (24 Plates) Plate No.																							
		2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
Anomalous Trichromasy																									
Deuteranomaly	7	43	43	0	14	72	14	57	0	14	29	0	14	14	0	0	0	14	14	0	14	0	57	29	14
Protanomaly	5	20	20	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0,	20	60	20	20
Dichromasy																									
Deuteranopia	5	0	0	0	0	20	0	20	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Protanopia	5	0	20	0	0	0	0	0	0	0	0	0	0	0	0	0	0	20	20	20	40	0	20	0	0
All types of defective color vision	22	18	23	0	5	27	5	23	0	5	9	0	5	5	0	0	0	9	9	5	14	5	36	14	9
		Ishihara Plates, American Optical Company (10 Plates) Plate No.																							
		5	6	11	12	19	20	41	42											33	34				
Anomalous Trichromasy																									
Deuteranomaly	7	86	43	0	43	72	0	72	57	.....				.....						57	57				
Protanomaly	5	40	0	0	0	0	0	0	0	.....				.....						20	20				
Dichromasy																									
Deuteranopia	5	20	20	0	20	0	0	40	40	.....				.....						20	20				
Protanopia	5	40	0	0	0	0	0	0	0	.....				.....						0	0				
All types of defective color vision	22	50	18	0	18	23	0	32	27	.....				.....						27	27				

* Each plate is designated by a series number and a plate number as it appears in the edition under consideration.

row shows the percentages for the subjects with defective color vision as a group.

The following statements summarize the more obvious and significant changes found in the same plate as reproduced in the four editions and the effect of these changes on the percentage of subjects passing each plate:

Series 1.—The plates of this series are the most significantly changed in the later editions. They have been improved in the seventh and ninth editions but not in the American Optical Company's compilation. In the fifth edition the chief defect lies in the fact that the background disks (green) are too light and too uniform in value, or brightness. As was pointed out in the former report,[1] these plates fail to detect a majority of the subjects with the protanopic type of defective red-green vision because this type tends to see the "normal" digit, which is composed of dominantly reddish disks, as a dark pattern on a lighter background. In the seventh and ninth editions, more dark green disks are interspersed among the background disks, with the result that this criterion of brightness is no longer available to protanopes. These plates seem to be more critical for subjects of the deuteranomalous type also. In the American Optical Company's test, the background values used in the seventh edition are fairly well reproduced in the plates of series 1, but for some unknown reason the colored disks comprising the digit are lighter in value, lower in chroma and less blue in hue than in the seventh edition. The result is a much poorer plate for detection of the defect in color vision of subjects of the deuteranopic type, who tend to see the "normal" digit as a light pattern on a darker background. This plate illustrates the care that must be exercised when one is making polychromatic plates for testing defects in color vision to prevent any brightness clues from influencing the results.

Series 2.—This series of plates as reproduced in the fifth and seventh editions is failed by all the subjects with defective color vision tested. As reproduced in the ninth edition and the American Optical Company's test, it is less selective in the case of deuteranomalous and deuteranopic subjects, apparently owing to a poor reproduction in both value and hue of the pigments used to form the digits.

Series 3 and 4.—Our statistics show no significant difference in the results obtained with the plates of these series for the editions compared except that, as is usually the case, the two digit plates, which appear in the seventh and ninth editions, are more selective of defect in color vision than are the one digit plates, which appear in all the editions. These series are omitted from the American Optical Company's compilation, perhaps unfortunately, as they seem to be fairly good tests of defective red-green vision.

[1] Each plate is designated by a series number and a plate number as it appears in the edition under consideration.

Series 5.—In these plates, which contain a "hidden digit" supposedly seen only by subjects with defective color vision, the digit is composed of grayish blue and blue-red and blue-green disks of low chroma on a background of disks of high chroma, mostly yellow-red, yellow-green and dark yellow. In all but the fifth edition the digit stands out as a somewhat light, "ghostly" pattern, which is apparent to many, if not most, persons having normal color vision. This series is passed by the smallest percentage of subjects with defective color vision as reproduced in the fifth edition. It is more selective of the deuteranopic type as it is reproduced in the seventh and ninth editions and of the protanopic type as it is reproduced in the American Optical Company's test. It is our belief that this series of plates is the least satisfactory in the Ishihara test, because a considerable number of persons having normal color vision see the hidden digit, thus failing the plate, while many who have an extreme defect in color vision fail to see it, thus passing the plate.

TABLE 2.—*Significance of Performance Scores* for Subjects with Various Types of Defective Color Vision*

Type of Defective Color Vision	Number of Subjects	Average Score	Median Score	Range of Scores
	5th Edition			
Anomalous Trichromasy				
Deuteranomaly	7	20	17	0-58
Protanomaly	5	18	17	8-33
Dichromasy				
Deuteranopia	5	0	0	0
Protanopia	5	13	17	8-17
All types of defective color vision	22	14	17	0-58
	7th Edition			
Anomalous Trichromasy				
Deuteranomaly	7	18	17	0-33
Protanomaly	5	8	12	0-17
Dichromasy				
Deuteranopia	5	2	4	0- 4
Protanopia	5	4	0	0-17
All types of defective color vision	22	9	6	0-33
	9th Edition (British Reprint)			
Anomalous Trichromasy				
Deuteranomaly	7	19	21	0-42
Protanomaly	5	6	4	0-12
Dichromasy				
Deuteranopia	5	2	0	0- 8
Protanopia	5	5	4	0-17
All types of defective color vision	22	9	4	0-42
	Ishihara Plates, Americal Optical Company Test			
Anomalous Trichromasy				
Deuteranomaly	7	50	50	20-70
Protanomaly	5	8	0	0-30
Dichromasy				
Deuteranopia	5	18	10	0-50
Protanopia	5	4	0	0-10
All types of defective color vision	22	23	10	0-70

* Performance score is the percentage of the plates to which correct responses were given.

Series 6.—The percentages of subjects passing this series of plates do not vary significantly for the different editions. The value of these plates for classification as to the type of defective red-green vision will be considered in connection with table 3.

SIGNIFICANCE OF PERFORMANCE SCORES ON ENTIRE TEST

Table 2 shows the performance scores obtained on the entire test for each of the editions of the Ishihara test under consideration and for the 10 Ishihara plates in the American Optical Company's test. In this table are given for each type of defect in color vision (*a*) the average score achieved by the group, (*b*) the median, or middle, score for each group, and (*c*) the range of scores, from lowest to highest, achieved by the individual subjects within each group. A score of 100 indicates that correct responses were given to all the plates of the test; a score of 0, that no correct responses were given, and scores between 0 and 100 indicate the percentage of plates to which correct responses were given. As in table 1, the first four rows of figures under each edition give the data for each type of defective color vision, and the bottom row gives the data for the subjects with defective color vision as a group.

The following points are brought out in table 2:

1. A comparison of the average and median performance scores and the range of performance scores for the different types of defective color vision does not reveal notable differences in the fifth, seventh and ninth editions of the Ishihara test, in spite of the many changes that have been made in the individual plates and in the number of plates. This is because in the later editions some of the plates have been improved but others have been made less effective. The most significant difference is in the lower scores achieved by the protanopic type of subject on the seventh and ninth editions as compared with those obtained on the fifth, owing to the improvement of the plates of series 1. Little, if anything, seems to have been gained by doubling the number of test plates in the later editions.

2. No cleancut separation as to extent or type of defect can be based on the performance scores achieved in any of the editions. While in general the dichromats had lower scores than the anomalous trichromats, a majority of the latter group had scores between 0 and 17, the range which included all the dichromats tested. Scores on the Ishihara test cannot, therefore, be used to indicate either the extent or the type of defect in color vision of the person being tested.

3. The 10 Ishihara plates as reproduced in the American Optical Company test are less effective for detecting deuteranomalous subjects and deuteranopes than are the fifth, seventh and ninth editions of the

test. The scores for these subjects on the 10 plates are higher and the range of scores is significantly wider than on the original test. This indicates either a poor selection of Ishihara plates for inclusion in the American Optical Company's test or a poor reproduction of the plates selected. It is probable that both are contributive factors.

In the former study [1] of 106 persons (74 subjects with defective and 32 subjects with low normal color vision) emphasis was laid on the fact that a critical performance score of 60 on the fifth edition of the Ishihara test was found to provide a cleancut separation between the scores of persons with normal color vision and those with defective color vision. That is, no person with normal vision achieved a score below 75 and no person with defective color vision a score above 58. The number of subjects tested in the present study is too few to permit a similar determination of the critical score for the seventh and ninth editions of this test; also, no persons having low, but normal, color vision were included among those tested. It may be pointed out, however, that the small group of subjects with defective color vision used in the present study is fairly representative of the larger group used in the earlier study. This is seen in a comparison of the average and median scores and the range of scores obtained on the fifth edition by the larger group, which are given in table 2 of the former report,[1] with the scores obtained on the fifth edition by the smaller group, which are given in table 2 of the present report. This comparison shows (*a*) that the median score for subjects with each type of defective color vision is exactly the same in the larger and in the smaller group, (*b*) that the differences in the average scores for subjects with each type of defective color vision in the two groups are insignificant and (*c*) that the range of scores is exactly the same for the deuteranomalous subjects and essentially the same for the other types of subjects with defective color vision in the two groups. The range of scores is most different for the protanopes. This is due to the presence of 1 person in the larger group of protanopes (17) who passed 4 plates (both the plates of series 1 and 5), scoring 33, and of 3 persons who did not pass any of the plates, scoring 0. The 5 protanopes of the smaller group passed either 1 or 2 plates, scoring 8 and 17, respectively. Since no subject with defective color vision in the smaller group scored above 33 on the seventh edition or above 42 on the ninth edition and since there is no reason to expect persons with normal color vision to make lower scores on the seventh or the ninth edition than on the fifth edition, it seems permissible to conclude, at least until further data are available, that 60 can be taken as the critical performance score for the seventh and the ninth (British reprint) editions, as well as for the fifth edition of the Ishihara test. That is, persons who on any of these editions score below 60 can be said as have defective color vision.

As was stated in the previous report, the "Pseudo-Isochromatic Plates for Testing Color Perception," distributed by the American Optical Company, was included in the full battery of tests given our larger group of subjects, on the basis of which the classification as to type of defect in color vision was made. We have available, therefore, the results on the 10 Ishihara plates included in that test for 74 subjects with defective color vision and for 32 subjects with low normal color vision. Space will not be taken to present these results. An analysis of the data, however, shows that there is considerable overlapping of the scores attained not only among the subjects with the various types of defective color vision but between the subjects with defective color vision and the subjects with low normal color vision. For example, scores for the 23 deuteranomalous subjects ranged from 10 to 100; scores for the 12 protanomalous subjects, from 0 to 30; scores for the 15 deuteranopes, from 0 to 50, and scores for the 17 protanopes, from 0 to 10. The range of scores for the 74 persons with defective color vision is 0 to 100, and the range for the 32 subjects with low normal color vision, 60 to 100. It is obvious, then, that the American Optical Company's Ishihara plates, considered alone, do not furnish a critical score to differentiate persons with normal from persons with defective color vision, as is the case, according to our data, for the fifth edition of the Ishihara test and, in all probability, for the seventh and ninth (British reprint) editions.

CLASSIFICATION AS TO DEUTERANOPIA AND PROTANOPIA, DEUTERANOMALY AND PROTANOMALY

So far we have discussed performance scores on different editions of the Ishihara test both as a means of detecting the presence of a defect in color vision and as a means of classifying the type of defect, and we have shown that the score achieved is adequate to separate subjects with defective color vision from subjects with normal color vision when the test is properly administered, but that it is not adequate to perform the equally important task of classifying the type and the extent of the defect. It remains to discuss the type of response to certain plates as reproduced in the different editions as a clue to this classification.

In the Ishihara test the plates of series 6 are the only ones designed for this purpose. There are 2 plates of this type in the fifth edition, 4 plates each in the seventh and the ninth edition and none in the American Optical Company's test. In these plates a double digit is presented (*26*, for example, on the first plate of series 6 in each edition). The left hand digit is composed of red disks, the right hand digit of red-purple disks and the background of gray disks. According to Ishihara, the subject with the deuteranopic type of defective red-green

vision will be able to read only the red digit, and the protanope, only the red-purple digit. Our data on the different editions have been analyzed to determine the effectiveness of these plates for this classification.

In scoring the responses to the plates, we used the criterion previously discussed.[1] That is, a subject was called "classified" as to type of defect by the edition in question when one digit was read correctly and the other was not seen at all or was read incorrectly. When both digits were read correctly, when neither was read correctly or when one was read incorrectly and the other not seen at all, the subject was called "not classified." In short, a "hit and miss" is necessary in order to utilize any plate of series 6 as a test for classification of the type of defect in red-green vision. It seems reasonable, also, to require a "hit and miss" on at least 50 per cent of the plates used for this purpose. The results obtained are shown in table 3.

TABLE 3.—*Classification as to Deuteranopia and Protanopia, Deuteranomaly and Protanomaly*

Type of Defective Color Vision	Number of Subjects	Classification by at Least 50% of Plates		
		Correctly Classified, %	Incorrectly Classified, %	Not Classified, %
5th Edition				
Anomalous Trichromasy				
Deuteranomaly	7	86	0	14
Protanomaly	5	80	0	20
Dichromasy				
Deuteranopia	5	100	0	0
Protanopia	5	60	0	40
7th Edition				
Anomalous Trichromasy				
Deuteranomaly	7	57	0	43
Protanomaly	5	40	20	40
Dichromasy				
Deuteranopia	5	100	0	0
Protanopia	5	60	0	40
9th Edition (British Reprint)				
Anomalous Trichromasy				
Deuteranomaly	7	86	0	14
Protanomaly	5	60	0	40
Dichromasy				
Deuteranopia	5	100	0	0
Protanopia	5	60	0	40

The following points are brought out in table 3:

1. The greatest number of subjects was correctly typed by the plates of series 6 as reproduced in the fifth edition, the next greatest number by the plates as reproduced in the ninth edition (British reprint) and the smallest number by the plates as reproduced in the seventh edition. These differences occur only in the number of anomalous trichromats successfully typed. All three editions give the same results for dichromats.

2. The plates are adequate to classify deuteranopes alone in all editions compared.

CONCLUSIONS

The following conclusions concerning the editions of the Ishihara test studied seem justified:

1. A comparison of the average scores and the range of scores for the different types of deficiency in color vision does not reveal notable differences in the fifth, seventh and ninth (British reprint) editions of the Ishihara test, in spite of the changes made in the number of plates and in the plates themselves, some of which are improved and some of which are made less effective. The most significant difference is in the results for the observers of the protanopic type which are due to the improvement of the plates of series 1 in the seventh and ninth editions.

2. Properly administered, the three editions of the Ishihara test afford a good rough device for screening persons with defective from persons with normal color vision if a performance score of 60 is taken as the critical score. In the groups tested in this study and in the former study of the fifth edition of the test,[1] no person with defective color vision scored more than 58 and none with low normal color vision less than 75. A critical score cannot, however, be established for the 10 Ishihara plates reproduced in the American Optical Company's test. Tested with this group of plates, some subjects with defective color vision passed all the plates, scoring 100; and some with low normal color vision passed only 6 of the plates, scoring 60.

3. No analysis as to type or extent of defect in color vision can be based on performance scores.

4. The plates of series 6 as reproduced in the fifth edition are the best for correctly classifying the type of anomalous trichromasy, those of the ninth edition the next best and those of the seventh edition the poorest. All three editions give the same classification of the type of dichromasy.

5. Nothing seems to be gained by doubling the number of plates, as is done in the seventh and ninth editions.

6. Other things being equal, plates bearing two digits afford better tests of defective color vision than plates having only one digit.

In brief, the general conclusions drawn from a study of a larger number of subjects for the fifth edition of the Ishihara test hold also for the seventh and ninth (British reprint) editions but not for the Ishihara plates as reproduced in the American Optical Company's test.

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EDEMA OF CORNEA PRECIPITATED BY QUINACRINE (ATABRINE)

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GENERAL CONSIDERATIONS

THE avascularity and transparency of the cornea permit study of early pathologic alterations to a degree not possible in other tissues. The slightest edema or most minute infiltration causes immediate changes in transparency. Alteration in the colloidal properties and the water content of the "corneal gel" leads to increased dispersion and refraction of light and augmentation of the normal Tyndall phenomenon, e. g., increases in relucency. It must be remembered that what is observed grossly or with the slit lamp and corneal microscope is the alteration in optical phenomena which result from changes in the tissues.

According to Fischer,[1] the normally clear cornea contains 76 per cent of water, and an additional 10 per cent may lead to clouding. When the fluid is gathered in droplets the light is irregularly dispersed, producing a relucent haze. As it affects the epithelium, this is commonly called "bedewing." This physical process of imbibition is completely reversible.

Edema forms the most common clinical pathologic manifestation of the corneal epithelium and occurs in nearly all corneal disturbances, both inflammatory and degenerative. It may be seen in conjunction with edema of deeper layers of the cornea. Duke-Elder [2] listed the common causes of corneal edema as including trauma, inflammation, degeneration and increased intraocular tension. Injury may be anatomic or physiologic; irrigation with distilled water or instillation of cocaine will produce edema of the epithelium. In glaucoma the elevated intraocular pressure is thought to force an increased amount of aqueous into the corneal tissue through the trabeculae at the angle of the anterior chamber.

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1. Fischer, cited by Duke-Elder,[2] p. 1845.

2. Duke-Elder, W. S.: Textbook of Ophthalmology, London, Henry Kimpton, 1939, vol. 2, p. 1846.

Berliner [3] mentioned interference with the antidromic impulses of the corneal nerves as a basis for epithelial edema, presumably through the accumulation of cellular metabolites. He also included allergy as a possible factor in such corneal changes. Finally, Duke-Elder stated that constitutional causes may be responsible for corneal edema. He cited reports by Aubineau [4] and, later, Marbaix [4] describing cases of this type in patients with elevated blood cholesterol. The lipid imbalance was thought to be the causative factor, and the corneal edema subsided with appropriate dietary treatment.

CLINICAL ASPECTS

During the past eighteen months a number of patients have been seen in the southwest Pacific area with bilateral haziness of the cornea of obscure origin. During the eight months from August 1944 through March 1945, inclusive, 4 such patients were studied in some detail at the hospital at which we are stationed. Examination with the slit lamp and the biomicroscope disclosed innumerable fine granular opacities evenly dispersed over the area of the cornea. These were apparently located primarily in the epithelium and, to a lesser extent, in the underlying superficial layers of the corneal parenchyma. The clinical picture was that of bilateral superficial corneal edema, and, as might be expected, the process was completely reversible. There were no associated signs of ocular inflammation, and there were no changes suggestive of glaucoma. Each of these patients was receiving the required protective dose of quinacrine (atabrine).

REPORT OF CASES

CASE 1.—An infantry private aged 20 noticed gradually increasing blurring of vision, beginning about July 27, 1944, while on jungle patrol in Aitape, New Guinea. He had no associated systemic complaints and no ocular irritation, pain, redness or conjunctival discharge. The impairment of vision was present at all distances and was experienced particularly at night, when there was a pronounced dispersal of lights. He noted no floating spots before the eyes and no defects of the visual fields. There was no history of a previous similar episode. The patient had never worn glasses, and vision had been excellent.

He had been in the tropics only one month prior to onset of this complaint. There was no history of injury to the eyes or of undue exposure to brilliant sunlight, dust or irritants. For four weeks his diet had consisted of C rations, with no fresh foods.

The only medicament received by the patient was quinacrine hydrochloride, and he had been taking 1 tablet (0.1 Gm.) daily for about six weeks.

On August 9 he was admitted to an evacuation hospital and was transferred to a station hospital at this base. Vision was recorded as 20/50 —2 in the right

3. Berliner, M. L.: Biomicroscopy of the Eye, New York, Paul B. Hoeber, Inc., 1943, vol. 1, p. 393.

4. Cited by Duke-Elder,[2] p. 1848.

eye and 20/40 —3 in the left eye. There was described a diffuse haziness of the substantia propria as the only positive finding. Treatment included administration of multivitamins, instillation of atropine and application of hot compresses. Vision gradually improved to 20/20— in each eye, and the patient was discharged to duty. However, at this time there was still some blurring of vision, which was most conspicuous at night.

About September 25 he again noticed gradually increasing visual impairment of the type previously experienced. He was again hospitalized on October 9 and was returned to the station hospital. Vision on this second admission was recorded as 20/40 —2 in the right eye and 20/40 in the left eye.

Consultation at this general hospital then disclosed a diffuse haziness of the corneas due to finely dispersed punctate opacities, which seemed to be most numerous in the superficial corneal layers. The epithelial surface, however, was smooth, and at that time there was no staining with fluorescein. There was no evidence of intraocular inflammation; in each eye the anterior chamber, iris, lens, vitreous and fundus were normal.

There was no tenderness on palpation, and the intraocular tension was normal as read at various hours of the day.

Determination of the visual fields disclosed normal peripheral limits: The blindspot measured 6 by 8 degrees in the right eye and 6 by 8 degrees in the left eye (1 mm. white test object at 33 cm.). There was no significant error of refraction.

A complete medical investigation revealed no evidence of systemic disease. Consultations with members of the dental, otolaryngologic and urologic staffs revealed no foci of infection. Blood counts and urinalysis gave normal results; the Kahn reaction was negative, and a smear revealed no malarial organisms. Cutaneous reactions were negative to tuberculin (purified protein derivative) in both dilutions. A patch test for quinacrine was negative. Treatment at the station hospital again consisted in the use of atropine, hot compresses and multivitamins. After two months' observation vision had improved only to 20/30 in each eye.

On Jan. 4, 1945 the patient was transferred to this general hospital, with visual acuity of 20/30 in the right eye and 20/30 in the left eye. Examination with the slit lamp still showed diffuse haziness of each cornea due to a fine stippling of punctate opacities, located largely in the most superficial layers. Again there was no staining with fluorescein, and the eyes were otherwise normal.

No causative factor for this corneal edema had been found after extensive investigation and observation. The patch test for quinacrine had been negative, and the patient had continued to receive the usual 0.1 Gm. daily dose of the drug. In an attempt to rule out idiosyncrasy to quinacrine it was decided (1) to stop the drug for one month and (2) to administer larger doses of quinacrine.

The patient was given no quinacrine from January 4 through February 3. During this interval vision improved to 20/20 in the right eye and 20/20 in the left eye; but there were still a few residual opacities, and vision continued to be somewhat blurred, with dispersal of lights at night.

On February 4 an intensive course of quinacrine therapy, comparable to that used in treatment of malaria, was started. This regimen consisted in administration of divided doses of the drug, totaling 1.2 Gm. the first day, 0.8 Gm. the second day and 0.4 Gm. on each of the succeeding four days. He was then continued on a regimen of 0.2 Gm. daily through February 16.

For eight days after the beginning of quinacrine therapy there was no appreciable change in the corneal condition. On February 12 the patient noticed

increasing blurring of vision, but again without any redness or irritation of the eyes. On February 16 vision had decreased to 20/100 in the right eye and 20/100 in the left eye. Examination showed no conjunctival injection, but the cornea was diffusely hazy, giving an appearance of ground glass. The opacities were of the type previously described but much more dense, and on this occasion there were many fine punctate erosions of epithelium, which stained with fluorescein. After quinacrine therapy was discontinued, on February 16, the cornea gradually cleared; e. g., vision was 20/40 in each eye on February 23. By March 17 it was 20/20 in each eye, and there was only slight dispersal of lights at night. After two months without quinacrine vision was 20/20 in each eye, and the patient noted only the slightest dispersal of lights. The cornea was then normal on all examinations.

While receiving the intensive course of quinacrine treatment, the patient experienced some nausea, anorexia and slight abdominal distress, but he did not vomit. He had moderate malaise and lost 5 pounds (2.3 Kg.) in weight. Examination showed no abdominal distention and no enlargement or tenderness of the liver. The scleras were not discolored. However, there were a moderately elevated icteric index, of 15, and impairment of hepatic function as revealed by the hippuric acid excretion test, e. g., an excretion of 1.6 Gm. of hippuric acid and 1.1 Gm. of benzoic acid, per hundred cubic centimeters. The medical consultant made a diagnosis of "hepatitis with subclinical icterus." The sedimentation rate remained normal, as did the serum protein content. After discontinuation of the drug, on February 16, the anorexia and vague abdominal distress gradually subsided, and the patient had more than regained the lost weight at the end of four weeks. On March 27 the hippuric acid excretion test showed improvement, e. g., an excretion of 3.2 Gm. in terms of hippuric acid and of 2.2 Gm. in terms of benzoic acid, per hundred cubic centimeters, and the general physical condition was again entirely normal.

Case 2.—A 20 year old private in the Quartermaster Corps noticed gradually increasing blurring of vision, beginning about Aug. 1, 1944, while en route from Oro Bay to Finschhafen, New Guinea. There were no associated systemic complaints and no ocular irritation, pain, redness or conjunctival discharge. The visual impairment was present at all distances and was particularly troublesome at night, when there was pronounced dispersal of lights. He observed no floating spots before the eyes and no defects in the visual fields. There was no history of a previous similar episode.

The patient had been in the tropics only one month prior to the onset of this complaint. There was no history of injury to the eyes or of undue exposure to brilliant sunlight, dust or irritants. For seven weeks prior to the onset of visual disturbance his diet had consisted of C rations, with no fresh meats, fruits or vegetables. The only medicament which he had received was quinacrine hydrochloride, and he had been taking 1 tablet (0.1 Gm.) of this drug daily for approximately six weeks.

On admission to this general hospital, on August 3, vision was 20/70 in the right eye and 20/100 in the left eye; with correction it was 20/50 in the right eye and 20/70 in the left eye. Examination showed diffuse haziness of each cornea, due to a fine stippling of punctate superficial opacities. Examination with the slit lamp and corneal microscope indicated that these were located primarily in the basal layers of the corneal epithelium. The epithelial surface, however, was smooth, and at that time there was no staining with fluorescein. There was no conjunctival or circumcorneal injection and no evidence of intraocular inflammation; the ocular media were apparently clear and the fundi normal.

There was no tenderness on palpation, and the intraocular tension was normal on repeated readings at various hours. The visual fields showed normal peripheral limits, and the blindspots were of average size, measuring 5 by 7 degrees in the right eye and 5 by 7 degrees in the left eye (1 mm. white test object at 33 cm.). Refraction indicated a moderate degree of compound myopic astigmatism, as follows: right eye: —1.00 D. sph. ⌒ —0.75 D. cyl., axis 90; left eye: —1.00 D. sph. ⌒ —0.75 D. cyl., axis 90.

Complete medical investigation on his admission disclosed no evidence of systemic disease. Dental, otolaryngologic and urologic consultants reported no foci of infection. Blood counts and urinalyses showed nothing abnormal; the Kahn reaction of the blood was negative, and a smear revealed no malarial organisms. Cutaneous reactions were negative to tuberculin (purified protein derivative) in both dilutions. A patch test with powdered quinacrine gave a negative reaction.

The patient was not given any ocular treatment for three weeks, and with correction vision gradually improved to 20/30 in each eye. There was some fluctuation in the density of the opacities and the visual acuity from day to day. Quinacrine was then discontinued for four weeks, and vision improved to 20/20 in each eye, but there was still slight blurring, with dispersal of lights at night. Quinacrine therapy was resumed, with 1 tablet (0.1 Gm.) daily for two weeks, without apparent alteration in the residual corneal edema; and on October 3 the patient was discharged to duty. About one month later he noticed a gradual increase in blurring of the type previously experienced. During the succeeding eight weeks the visual impairment became so pronounced as to interfere seriously with the performance of duty, and he was readmitted to this general hospital on December 29. Vision with correction was then 20/40 in each eye, and examination showed fine superficial corneal opacities, identical with those described on the original admission. The patient was given polyvitamins, 2 tablets, and riboflavin, 2 mg., three times daily.

No causative factor for this corneal edema had been found after extensive investigation and observation. The patch test had been negative for quinacrine, and the patient had continued to take the usual 0.1 Gm. daily dose of the drug. In an attempt to rule out idiosyncrasy to quinacrine, it was decided (1) to stop the drug for one month and (2) to administer larger doses of quinacrine.

No quinacrine was received from Jan. 4, to Feb. 4, 1945. During this period vision with glasses again improved, being 20/20 — in each eye. However, there still remained the occasional residual opacities, with subjective blurring and dispersal of lights at night.

On February 4 an intensive course of quinacrine therapy, comparable to that used in the treatment of malaria, was started. This regimen consisted in divided doses of the drug, totaling 1.2 Gm. the first day, 0.8 Gm. the second day and 0.4 Gm. on each of the succeeding four days. The patient had some nausea and vomiting, particularly on the first two days of treatment, but he was able to retain the full six day dose of quinacrine; the dose was then reduced to 0.2 Gm. daily through February 16.

For six days after beginning quinacrine therapy there was no change in the corneal condition, but on February 10 he noticed increasing blurring of vision, with slight irritation, redness and tearing. By February 16 vision with correction had decreased to 20/70 in the right eye and 20/50 —1 in the left eye. Examination showed moderate injection of the conjunctiva with diffuse superficial haziness of the cornea. However, there were now many punctate erosions of the epithelial surface, which stained with fluorescein and were not present with previous episodes of corneal edema. After discontinuation of quinacrine on February 16, corneal

edema gradually subsided, and vision had improved again to 20/20 in each eye by February 26. However, the residual punctate opacities and a few erosions of the epithelium were slow in clearing, and after eight weeks an occasional punctate erosion could still be detected with the slit lamp. The cornea was now clearer than at any time during the past eight months, and the patient stated that the dispersal of lights at night had almost completely disappeared.

On February 4 and 5, at the beginning of the course of quinacrine treatment, the patient was nauseated and vomited several times. He complained of increasing anorexia, malaise and tenderness in the right upper quadrant of the abdomen but had no further vomiting. He had lost at least 10 pounds (4.5 Kg.) in weight by February 23, when examination disclosed moderate abdominal distention and ascites, with a fluid wave. The liver was enlarged and tender, extending 2 fingerbreadths below the costal margin. The scleras were never icteric. Laboratory tests reported an elevated corrected sedimentation rate of 26 mm. in one hour and reduced excretion of hippuric acid: 1.9 Gm. in terms of hippuric acid and 1.3 Gm. in terms of benzoic acid, per hundred cubic centimeters; the icteric index was 12. A diagnosis of "hepatitis with subclinical icterus" was made by the medical consultant. With rest in bed, the patient showed steady clinical improvement over a two week period. The anorexia, malaise and abdominal discomfort disappeared. By March 10 the liver was no longer enlarged or tender and there was no ascites. However, the increased sedimentation rate and the diminished excretion of hippuric acid persisted without change for two months, although the patient had no abdominal complaints and clinically seemed to be fairly normal.

CASE 3.—A 29 year old infantryman noticed sudden onset of blurring of vision in each eye on Aug. 21, 1944, at Aitape, New Guinea. During the previous night he had complained of transient bifrontal headache but had no other symptoms suggestive of systemic disease. There was no associated ocular irritation or pain and no redness, tearing or conjunctival discharge. The impairment of vision was present at all distances and was most troublesome at night, when there was a pronounced dispersal of lights. He observed no floating spots before the eyes and no defects of the visual fields.

The patient had served nineteen months in tropical New Caledonia and the Solomon Islands and five weeks in New Guinea, after a three month interval in New Zealand. His general health had been excellent. There was no history of injury to the eyes or of undue exposure to brilliant sunlight, dust or irritants. The diet had consisted largely of C rations, with only occasional fresh meat or eggs.

Quinacrine hydrochloride was the only medicament received. He had been taking this drug for twenty-one months, as follows: November 1942 to July 1943, ½ tablet (0.05 Gm.) daily; July 1943 to July 1944, 1 tablet (0.1 Gm.) daily, and during the latter part of July and the month of August 1944, 2 tablets (0.2 Gm.) daily. The last period was from the date of landing in New Guinea until his admission to the station hospital, on Aug. 30, 1944. The dose of quinacrine hydrochloride was then reduced to 0.1 Gm. daily during hospitalization.

At the station hospital, on September 1, vision was recorded as 20/70 in each eye. There were described fine granular superficial opacities of each cornea, giving a steamy appearance. The patient was evacuated to this general hospital with a diagnosis of "corneal edema."

On his admission, on September 4, vision had improved to 20/40 in each eye. Examination revealed diffuse haziness of each cornea due to innumerable fine punctate opacities. Examination with the slit lamp and biomicroscope showed

these to be located in the superficial layers of the cornea, and primarily in the epithelium. At that time, however, the epithelial surface was smooth and did not stain with fluorescein. There was no evidence of intraocular inflammation; the ocular media were apparentlly clear and the fundi normal. There was no tenderness on palpation. Intraocular tension was normal on repeated examinations at various hours. Examination of the visual fields indicated normal peripheral limits; the blindspot measured 7 by 5 degrees in the right eye and 7 by 5.5 degrees in the left eye (1 mm. white test object at 33 cm.).

Complete medical investigation on his admission disclosed no evidence of systemic disease. Consultations revealed no foci of infection in the sinuses, the teeth or the prostate gland.

Laboratory tests on admission, including blood counts, determination of the sedimentation rate and urinalysis, gave normal results. The Kahn reaction of the blood was negative, and a smear revealed no malarial organisms. Cutaneous reactions were negative to tuberculin (purified protein derivative). A patch test for quinacrine gave a negative reaction.

The patient was given no treatment during the first week in this hospital, and vision had improved to 20/20 in each eye by Sept. 11, 1944. It was at first thought that he could be discharged to duty, but the subjective blurring persisted, with fluctuations, vision varying from 20/20 to 20/30 in each eye. He was given 2 capsules of polyvitamins and 2 mg. of riboflavin three times daily over a ten week period, without clearing of the residual corneal edema.

In late November 1944 he began to experience sporadic anorexia, vague epigastric discomfort and "heart burn." Repeated examinations of the abdomen revealed nothing abnormal. Because of persisting symptoms, a series of roentgenographic studies of the gastrointestinal tract were made on Jan. 5, 1945, but no abnormality of the stomach or the duodenum was disclosed.

No causative factor for this corneal edema had been found after extensive investigation and observation. The patch test for quinacrine had been negative, and the patient had continued to receive the usual 0.1 Gm. daily dose of the drug. In an attempt to rule out idiosyncrasy to quinacrine, it was decided (1) to stop the drug for one month and (2) to administer larger doses of quinacrine.

No quinacrine was administered from Jan. 4 through Feb. 3, 1945. There seemed to be further subjective clearing of vision, which was again recorded as 20/20 in each eye. Only occasional punctate opacities remained at the end of this period. The vague abdominal complaints likewise largely subsided.

An intensive course of quinacrine therapy, comparable to that used in treatment of malaria, was then started. This regimen consisted in administration of 1.2 Gm. the first day, 0.8 Gm. the second day and 0.4 Gm. on each of the succeeding four days. However, he began to vomit on the second day of treatment, and on the fourth day administration of the drug was discontinued because of inability to retain the medicament. There was aggravation of abdominal complaints.

There was no change in the corneal condition for eleven days after administration of the drug was started, but on February 15, seven days after quinacrine had to be discontinued, there began to develop blurring vision, due to increasing numbers of the fine punctate opacities. On February 18 visual acuity was 20/40 in each eye, and on February 22 it had dropped to 20/50 in the right eye and 20/70 in the left eye. Again the slit lamp showed innumerable fine superficial corneal opacities involving the epithelium and the superficial layers of the stroma. For the first time, however, there were many superficial punctate erosions of the epithelium, which stained with fluorescein. Thereafter vision steadily improved, as the density of the opacities decreased. On February 25 vision was 20/40 in

each eye; on February 27, 20/30, and on March 5, 20/20. On April 1 vision was a full 20/20 in each eye and no corneal opacities could be detected with the ophthalmoscope or the slit lamp.

During this same period the patient's abdominal complaints became accentuated, with pronounced cramping, nausea, vomiting and distention. On February 19 the liver was enlarged and tender and there was definite ascites. Clinical icterus was present, and numerous spider nevi were evident over the face and trunk. Laboratory tests revealed icteric indexes averaging 40 and total plasma proteins of 6.1 Gm. with 2.6 Gm. of albumin and 3.5 Gm. of globulin, per hundred cubic centimeters. The ascites rapidly increased, and diuresis was not obtained with intravenous injection of 50 per cent dextrose, serum albumin and mercurophylline. Abdominal paracenteses were performed on March 13 and again on March 23, 1945, 4,000 cc. of clear fluid being obtained on each occasion. The patient ran a moderate fever, with elevation of temperature as high as 101 F.; this was not appreciably affected by treatment with penicillin. He was given a preparation of vitamin K in large doses to combat persistent and recurrent bleeding from the gums and from a spider nevus on the right cheek.

Finally, on March 30, diuresis was induced, and the ascites gradually subsided without further treatment. The icteric index was 35 on April 4, and the total plasma proteins measured 6.6 Gm., with 3.5 Gm. of albumin and 3.3 Gm. of globulin, per hundred cubic centimeters. By May 1 the ascites had completely disappeared, and the icteric index had dropped to 12. The patient's general condition was much improved, and his convalescence from the severe hepatitis was progressing satisfactorily.

CASE 4.—A 29 year old corporal, a wireless operator, had rapidly increasing blurring of vision in each eye, which began on Oct. 17, 1944. He had no associated systemic complaints and no ocular irritation, pain or redness or conjunctival discharge. The impairment of vision was present at all distances and was particularly pronounced at night, when there was marked dispersal of lights. There were no floating spots before the eyes, and no defects of the visual fields were noted.

Prior to onset of this complaint the patient had served eight months in New Guinea. In March 1944, one month after arriving in the tropics, he experienced a similar attack of blurred vision, for which he was treated at a field hospital. His vision gradually improved without specific treatment, and he was discharged to duty in six weeks. However, there was residual blurring of such degree that he was unable to resume his previous duties as wireless operator.

There was no history of injury to the eyes or of undue exposure to brilliant sunlight, dust or irritants. His diet had consisted of the usual C rations, with no fresh foods.

The only medicament received by the patient was quinacrine hydrochloride, and he had been taking 1 tablet (0.1 Gm.) of the drug daily during the eight months of tropical service.

On Oct. 19, 1944 he was admitted to a station hospital; visual acuity was recorded as 20/50 in each eye and was not improved with lenses. Examination disclosed a diffuse granular haziness of each cornea. Study with the slit lamp and corneal microscope in consultation at this general hospital showed that these finely dispersed punctate opacities were located in the superficial corneal layers, but the epithelial surface was smooth and did not stain with fluorescein. There was no evidence of intraocular inflammation; in each eye the anterior chamber, iris, lens, vitreous and fundus were of normal appearance.

There was no tenderness on palpation, and the intraocular tension was not elevated. The visual fields were grossly normal. Refraction indicated moderate hyperopic astigmatism, as follows: right eye: + 2.25 D. sph. ⌒ + 0.50 D. cyl., axis 95; left eye: + 2.00 D. sph. ⌒ + 0.50 D. cyl., ⌒ axis 85. Vision was not improved with lenses.

The patient was given polyvitamins and riboflavin. Atropine was instilled in each eye, and hot compresses were applied.

On the day following his admission vision had dropped to 10/200 in each eye and corneal opacites were much more dense. Thereafter there was gradual improvement, with visual acuity of 20/200 on the fourth day and 20/40 on the ninth day after admission. There continued to be some fluctuation in density of the opacities, and after two months vision had not improved beyond 20/30 in each eye and there were residual corneal opacities.

After the first few days of hospitalization the patient began to complain of vague abdominal distress and malaise. General examination and medical consultation revealed nothing of significance at this time. Initial laboratory tests disclosed only moderate secondary anemia, with 3,770,000 red blood cells and 75 per cent hemoglobin; the urine was normal, and the icteric index was 6. The patient was treated symtomatically with tincture of belladonna and phenobarbital, without relief. On December 11 Necator americanus was found in the stool, and the patient was given tetrachloroethylene as a vermifuge; subsequent examinations of the stool were negative for the parasite.

By December 21 epigastric distress had become severe, and abdominal distention, ascites and clinical icterus had developed. Treatment included large doses of a preparation of vitamin K and intravenous injections of dextrose, plasma and whole blood.

The patient's general condition seemed somewhat improved, and on Jan. 11, 1945 he was transferred to this general hospital. Laboratory tests were then reported as showing 2,450,000 red blood cells, 50 per cent hemoglobin and 3,950 white blood cells. The corrected sedimentation rate was consistently elevated, e. g., 21 to 26 mm. in one hour. Determinations of the serum proteins indicated a reversed albumin-globulin ratio, the total proteins measuring 6.6 Gm., with 2.6 Gm. of albumin and 4.0 Gm. of globulin, per hundred cubic centimeters. Intensive therapy was continued, with repeated blood transfusions and intravenous injections of plasma, 50 per cent dextrose and mercurophylline. The ascites and edema gradually subsided, but by February 2 the icteric index had risen to 170. The patient had recurrent and persistent bleeding from the nose, gums and rectum, and despite supportive treatment there were increasing depression and drowsiness. He finally became stuporous and lost consciousness one day before his death, on February 19. The final clinical diagnosis was "acute hepatitis with jaundice, cause undetermined."

Quinacrine therapy had been discontinued in mid-December, when abdominal complaints became pronounced; at that time vision was 20/30 in each eye, and the residual corneal edema persisted. By Jan. 27, 1945 vision had cleared to approximately 20/20 in each eye. Repeated subsequent examinations with the ophthalmoscope and hand slit lamp during this terminal phase of his illness failed to disclose any demonstrable corneal opacities.

Postmortem examination was performed by the pathologist at this hospital, and a complete report was submitted to the Surgeon General. The pathologic diagnoses included (1) diffuse necrosis of the liver; (2) bile nephrosis; (3) splenomegaly (weight, 500 Gm.) with hyperemia and hyperplasia of the splenic

pulp; (4) intra-alveolar pulmonary hemorrhage; (5) generalized icterus, and (6) multiple subcutaneous hemorrhages.

The following description of the pathologic changes in the liver is quoted in detail from the autopsy report:

"The liver weighed 1,750 Gm. and measured 28 by 16 by 7 cm. The capsule was pale gray, smooth and translucent. The edges of the liver were sharp. The organ cut with normal resistance and showed a reddish brown, slightly bulging cut surface, in which the central veins of the hepatic lobules stood out prominently as red dots. Microscopic examination of sections taken through the liver revealed that the parenchyma was almost completely destroyed and the normal architecture greatly distorted. Only small groups of hepatic cells remained, and these were widely separated by edematous stroma. The parenchymal cells were undergoing all degrees of degenerative change, from pronounced cloudy swelling to complete necrosis. All the remaining hepatic cells were intensely bile stained. There was edema of the portal areas, but no proliferation of the fibrous connective tissue and only beginning multiplication of the bile ducts. There was no infiltration of inflammatory cells, either in the stroma of the portal areas or in the supporting tissue of the liver. There was hyperemia of the central veins and adjacent capillaries of the portal lobules."

ANALYSIS OF CASES

History.—Impaired vision was the only presenting complaint. The blurring was evident at all distances, and there was no apparent restriction of the visual fields; the condition was most troublesome at night, when there was a pronounced dispersal of lights. There was no associated ocular irritation, pain or redness or conjunctival discharge. In none of the cases was there a history of injury to the eyes or of undue exposure to brilliant light, dust or irritants. The diet had apparently been adequate, consisting largely of canned foods. It was found that all the patients had within two months been stationed in the United States or had been on extended leave in New Zealand, where ample fresh fruits, vegetables, meats and dairy products were avaiable.

Each of the 4 men was receiving quinacrine, and this was apparently the only medicament prescribed. Three of them had been taking the drug only four to six weeks prior to the initial visual disturbance. The fourth had taken quinacrine hydrochloride for twenty months, but seven weeks before he first noticed blurring of vision the usual dose of 0.1 Gm. had been increased to 0.2 Gm. daily.

Ocular Examination.—Visual acuity was impaired to about the same degree in the two eyes, as indicated in the individual case reports. On admission these patients showed a diffuse haziness of each cornea. The cornea had a granular appearance, due to innumerable minute punctate opacities evenly dispersed over its surface. Examination with the slit lamp and corneal microscope showed these delicate opacities to be located near the level of Bowman's membrane. There seemed to be increased relucency of the most superficial layers of the corneal parenchyma, as well as involvement of the deeper epithelial cells. At

that time the epithelial surface was smooth and did not stain with fluorescein. Ophthalmoscope study with a + 8.00 D. lens revealed the opacities as a fine granular stippling seen in silhouette against the fundus reflex.

There was no injection of the conjunctiva and no evidence of inflammation involving the aqueous, iris, lens, vitreous or fundus. The visual fields were normal in all respects. Repeated tonometric readings of intraocular tension taken at various hours of the day were within normal limits.

General Investigation on Admission.—In each case the general history and physical examination on admission disclosed no evidence of systemic disease. Consultations with members of the dental, otolaryngologic and urologic staff revealed no foci of infection. Initial laboratory tests, including complete blood counts and urinalyses, revealed an essentially normal condition; the Kahn reaction of the blood was negative, and smears revealed no malarial organisms. Cutaneous reactions were negative to tuberculin (purified protein derivative) in both dilutions. Patch tests with powdered quinacrine gave a negative reaction.

Course.—During the first weeks of hospitalization there seemed to be some improvement without specific treatment. Two of the patients were treated with atropine and hot compresses at another hospital, and all received large doses of polyvitamins and riboflavin, without apparent benefit. The residual edema and slight blurring fluctuated in intensity, never completely disappearing. The condition of 3 patients was so much improved that this minimal blurring, with dispersal of lights at night, was not considered a contraindication to discharge from the hospital. In each case the pronounced edema and blurring recurred, necessitating rehospitalization.

INVESTIGATION OF THE QUINACRINE FACTOR

All 4 patients had been receiving quinacrine hydrochloride prior to onset of the visual complaints. Patients 1, 2 and 4 had been under treatment with 0.1 Gm. daily for only four to six weeks; patient 3 had been taking 0.1 Gm. of quinacrine hydrochloride daily for twelve months, but this dose had been increased to 0.2 Gm. daily six weeks prior to the onset of visual complaints. These patients were examined regularly while continuing to receive the usual suppressive dose of 0.1 Gm. of the drug daily; they showed variations in density of the residual corneal edema with corresponding fluctuation in visual acuity, but vision never became completely clear and the punctate opacities never entirely disappeared.

The reactions in the patch tests for quinacrine were negative, but no cause for the corneal edema had been determined. In an attempt

completely to rule out toxicity due to quinacrine as a possible factor, it was decided (1) to stop the drug completely for one month and (2) to administer larger doses of quinacrine. Only patients 1, 2 and 3 were available for this investigation.

During the period in which no quinacrine was taken there were a slow but definite improvement in the corneal condition and further clearing of the slight visual impairment. However, a small amount of edema persisted, and there was visual disturbance, particularly noticeable in dispersal of lights at night.

These 3 patients were then given the intensive course of quinacrine therapy, consisting in administration of 1.2 Gm. the first day, 0.8 Gm. the second day and 0.4 Gm. on each of the succeeding four days. Patients 1 and 2 completed the full course of treatment, but patient 3 was unable to tolerate the drug, owing to persistent vomiting. Its administration was finally discontinued on the fourth day. The exact amount of the retained drug could not be determined.

In patients 1 and 2, who completed the full course, there developed pronounced corneal edema, beginning six and eight days, respectively, after the drug was started. In patient 3, who did not complete the course, the blurring and edema began eleven days after the initial large dose of quinacrine. This corneal edema was more intense than had previously been seen in any of these patients, and for the first time there were punctate erosions of surface epithelium. Quinacrine therapy was the only factor in their routine which was altered during this period.

HEPATIC FUNCTION

Impairment of hepatic function was a late occurrence in these patients, and in each it became apparent three to six months after the initial episode of visual disturbance. The medical investigation on the patient's admission had shown an essentially normal condition.

Patient 1 had no symptoms suggestive of hepatic dysfunction prior to taking the intensive course of quinacrine treatment. He had some nausea, anorexia, vague abdominal distress and loss of 5 pounds (2.3 Kg.) in weight with the larger dose of the drug but showed no enlargement or tenderness of the liver. The icteric index increased to 15, and excretion of hippuric acid dropped to 1.6 Gm. in terms of hippuric acid and to 1.1 Gm. in terms of benzoic acid. The medical consultant made the diagnosis of "hepatitis with subclinical icterus and impaired hepatic function as shown by the hippuric acid excretion test."

Patient 2, likewise, had no complaints indicative of impaired hepatic function before the dose of quinacrine hydrochloride was increased. With the intensive course he experienced nausea, vomiting, increasing anorexia, malaise, tenderness in the right upper abdominal quadrant and loss of weight of at least 10 pounds (4.5 Kg.). Examination showed

moderate abdominal distention and minimal ascites, with a fluid wave. The liver was enlarged and tender and was palpable 2 fingerbreadths below the costal margin. The corrected sedimentation rate was 26 mm. in one hour; the hippuric acid excretion test showed reduction to 1.3 Gm. per hundred cubic centimaters in terms of benzoic acid; the icteric index was 12. The medical consultant made the diagnosis of "hepatitis with subclinical icterus."

Patient 3 had vague abdominal complaints for about three months with no objective signs. On receiving larger doses of quinacrine, this patient had persistent vomiting, which necessitated discontinuation of the drug. He then complained of increasing abdominal distention, tenderness in the right upper quadrant, nausea and vomiting. The liver was large and tender; there were definite ascites and clinical icterus. Laboratory tests showed an average icteric index of 40 and total plasma proteins measuring 6.1 Gm., with 2.6 Gm. of albumin and 3.5 Gm. of globulin, per hundred cubic centimeters. A diagnosis of "severe hepatitis" was made by the medical consultant.

The fourth patient was not given the intensive course of quinacrine therapy. Severe hepatitis with clinical icterus and ascites had already developed before his transfer to this hospital. Laboratory tests revealed icteric indexes as high as 170, a reversed serum albumin globulin ratio, an elevated sedimentation rate and pronounced secondary anemia. Postmortem examination disclosed extensive diffuse necrosis of the liver.

INCIDENCE OF CORNEAL EDEMA

Corneal edema would seem to be a relatively infrequent manifestation of quinacrine sensitivity. While the symptoms are of such nature as to cause the patient to seek early medical assistance, the diagnosis may not be readily apparent to the untrained observer. The condition of a number of these patients has been initially diagnosed as "dystrophy," particularly when precision equipment was not available.

During the four months since this paper was originally submitted, we have examined 2 more patients with this type of corneal edema. In each of these patients the blurring of vision began a few weeks after he started to take quinacrine. Likewise, as in the original cases, the corneal edema subsided after use of the drug was discontinued. One of these patients was again given quinacrine, and the corneal edema recurred. Initial tests of hepatic function were made in each case and found to be within normal limits. Circumstances made it impossible to carry out a more complete or prolonged investigation of these patients, and for this reason the case reports are not presented in detail.

On the basis of verbal communications to us, it is estimated that at least 25 cases of corneal edema have been recognized in the Pacific

theater. These have been distributed through seven general hospitals and a corresponding number of smaller medical units.

COMMENT

That quinacrine may precipitate corneal edema in sensitive persons would seem to be clearly indicated.

It is of interest that in each of the patients available for prolonged study there apparently developed at least some degree of impairment in hepatic function.

During the period in which these patients were observed there was a relatively high incidence of "infectious hepatitis" in the Pacific area in which they were stationed. A considerable number of the patients who were hospitalized primarily for hepatic disease were carefully examined, and no instance of corneal edema was found. In the interval of eight months during which these studies were carried out there were 65 cases of "infectious hepatitis" in this general hospital, a ratio of about 14 per thousand admissions.

In interpreting the associated impairment of hepatic function in these patients with corneal edema, the presence of "infectious hepatitis" in the area must be considered. However, since in each of the 4 patients with this unusual form of corneal edema precipitated by quinacrine hepatic dysfunction also developed, the possibility that quinacrine might likewise be a contributing factor in the hepatic disease should be given further investigation.

SUMMARY

Four cases of bilateral superficial corneal edema are presented in detail.

Visual impairment was the only initial complaint. This blurring was of approximately the same degree in the two eyes, fluctuated in severity and was most noticeable with the dispersal of lights at night.

Each patient had been taking protective doses of quinacrine. Three had received the drug for only four to six weeks before the initial visual disturbance. One had been taking 0.1 Gm. of quinacrine hydrochloride for twelve months but had had the dose increased to 0.2 Gm. seven weeks prior to onset of blurring.

Visual acuity was variable, and in 1 instance vision dropped to 10/200 in each eye. Examination showed diffuse haziness of the corneas due to evenly dispersed punctate, superficial opacities. These opacities were located primarily in the superficial layers of the cornea, but on initial examinations the epithelial surface was smooth and did not stain with fluorescein. There was no evidence of ocular disease, and the general medical investigation on admission showed no systemic disease. The corneal edema and blurring of vision fluctuated in severity

while the patient was still receiving 0.1 Gm. of quinacrine hydrochloride, but the opacities never disappeared. Patch tests gave negative reactions for quinacrine.

Quinacrine was withheld from 3 patients for one month, and there was definite clearing of residual opacities. The patients were given large doses of the drug and exhibited pronounced corneal edema, beginning six to eleven days after the first large dose of quinacrine. This was similar to the edema previously observed, but generally more severe, and there was punctate staining of the surface epithelium. Quinacrine therapy was then permanently discontinued, and edema gradually subsided. At the end of one month vision with correction was approximately 20/20 in all cases. After eight weeks there were no demonstrable opacities in 2 cases, and in the third case only an occasional punctate opacity could be detected.

In each of these 4 cases of corneal edema some degree of hepatic dysfunction subsequently developed, beginning three to six months after the initial visual disturbance. In 2 cases there were subclinical icterus and impaired hepatic function, as shown by the hippuric acid excretion test; in the other 2 cases severe hepatitis developed, terminating fatally in 1 case.

We have made examination in 2 additional cases of corneal edema since the original reports were submitted. On the basis of verbal communications, it is estimated that at least 25 cases of this type of corneal edema have been seen in the Pacific area.

CONCLUSIONS

Quinacrine may precipitate corneal edema in the occasional sensitive person. This may occur with the minmal, 0.10 Gm., daily dose of the drug. A period of several weeks may intervene between the first dose of the drug and the initial visual disturbance. When larger doses of quinacrine are employed, this interval of lag may be reduced to a few days.

Further investigation of hepatic function is indicated in these patients with corneal edema precipitated by quinacrine.

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RETURN OF VISION IN TRANSPLANTED ADULT SALAMANDER EYES AFTER SEVEN DAYS OF REFRIGERATION

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NUMEROUS experiments on various types of salamanders, both larvae and adults, have shown that when the eye is grafted in the orbit immediately after it has been excised the transplant in most cases eventually recovers its visual function (Stone and associates [1]). In some of these experiments eyes of animals of different species were exchanged. The success of the experiments, indicated by return of vision, was due not only to an early revascularization of the grafted eye and the preservation of its essential tissues but to the capacity of regeneration possessed by these eyes.

However, the picture of regeneration in the grafted eyes of larvae was quite different from that in the transplanted eyes of adults. In the larvae (Stone [1a]; Stone, Ussher and Beers [1b]) all the parts of the grafted eye survive except for occasional loss of a few ganglion cells in the retina. The optic nerve could therefore regenerate rather rapidly from the severed stump connected with the retina. In the transplanted adult eye the retinal tissue degenerates rapidly with the exception of a peripheral ring of cells which survives along the ciliary margin. From these cells a new retina regenerates, and when differentiation is completed a new optic nerve emerges and passes along the pathway of the old degenerated

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1. (*a*) Stone, L. S.: Heteroplastic Transplantations of the Eyes Between Larvae of Two Species of Amblystoma, J. Exper. Zool. **55**:193-261, 1930. (*b*) Stone, L. S.; Ussher, N. T., and Beers, D. N.: Reimplantation and Transplantation of Larval Eyes in the Salamander (Amblystoma Punctatum), ibid. **77**: 13-48, 1937. (*c*) Stone, L. S., and Zaur, I. S.: Reimplantation and Transplantation of the Adult Eyes in the Salamander (Triturus Viridescens) with Return of Vision, ibid. **85**:243-269, 1940. (*d*) Stone, L. S., and Ellison, F. S.: Exchange of Eyes Between Adult Hosts of Amblystoma Punctatum and Triturus Viridescens, Proc. Soc. Exper. Biol. & Med. **45**:181-182, 1940. (*e*) Stone, L. S., and Cole, C. H.: Grafted Eyes of Young and Old Adult Salamanders (Amblystoma Punctatum) Showing Return of Vision, Yale J. Biol. & Med. **15**:735-754, 1943. (*f*) Stone, L. S.: Functional Polarization in Retinal Development and Its Reestablishment in Regenerating Retinae of Rotated Grafted Eyes, Proc. Soc. Exper. Biol. & Med. **57**:13-14, 1944.

nerve. The degeneration of the retina is initiated by a temporary loss of blood supply (Stone and Chace [2]). The reformation of a new retina can be brought about several times, as shown by Stone and Farthing,[3] who recorded that return of vision could be demonstrated four times in the same eye repeatedly transplanted.

In all the experiments just described the eyes were grafted to freshly denuded orbits in new hosts immediately after they had been removed from the donors. In 2 cases, however, described by Stone and Farthing [3] (pages 277 to 278), there was some delay before the transplanted eyes were finally attached to living hosts. When the eyes were being grafted for the third time the animals which were to have been the hosts for that period failed to revive from the anesthesia. Twenty-four to thirty-six hours after the operation the hosts were dead. The eyes, which had not yet shown prominent gross changes of degeneration, were immediately grafted to new hosts. Since they survived and were finally carried successfully through the four stages of transplantation, further experiments were devised to test the capacity of the adult eye of the salamander used to recover after it had been isolated from its blood supply for a long period before transplantation. To preserve the tissues in the graft during this period, the eyes were kept under refrigeration at various temperatures. The present paper will give a detailed account of the observations, some of which have appeared in a preliminary report (Stone [4]).

MATERIAL AND METHODS

Right and left eyes of adult salamanders (the vermilion spotted newt, Triturus viridescens) were carefully excised under the compound dissecting microscope in a manner already described by Stone and Zaur [1c] and placed in dishes on filter paper moistened with sterile Ringer solution. The dishes were then placed in a refrigerator under temperatures varying from 0 to 8 C., where they were left for periods of from two to fourteen days. Special care was taken to orient each eye on the filter paper to preserve the identity of all poles of the eye, so that later the graft could be normally oriented in the new host.

When the eye was transplanted, the right or the left eye, according to the demands of normal orientation, was excised from a new host, and into the freshly denuded orbit the refrigerated graft was placed in the normal orientation. The hosts were then placed on wet filter paper in cool chambers, where they remained quiet for twenty-four to thirty-six hours, during which time the eye healed sufficiently in place without the use of sutures. The animals were then placed

2. Stone, L. S., and Chace, R. R.: Experimental Studies on the Regenerating Lens and the Eye in Adult Triturus Viridescens, Anat. Rec. **79**:333-348, 1941.

3. Stone, L. S., and Farthing, T. E.: Return of Vision Four Times in the Same Adult Salamander Eye (Triturus Viridescens) Repeatedly Transplanted, J. Exper. Zool. **91**:265-285, 1942.

4. Stone, L. S.: Return of Vision in Transplanted Adult Salamander Eyes After Several Days of Refrigeration, Proc. Soc. Exper. Biol. & Med. **54**:44-45, 1943.

in water in separate aquariums, where they could be examined daily and records kept of the condition of the graft. A report will be given of the results of 70 experiments.

OBSERVATIONS

Delay Two Days; Temperature 8 C.—In 6 cases the right eye grafts were refrigerated for two days at 8 C. before they were transplanted. At the time these eyes were grafted their gross appearance had not changed much from that at the time they were enucleated. Ten days after the eyes were grafted the cornea in all cases was clear. The pupil was much contracted, and the pattern of iris pigmentation was changing. The normal sharp black band (fig. *1*) had become less distinct, and the yellow portion of the iris was darker. The lens was degenerating. The appearance was similar to that of an eye sixteen to twenty-one days after it had been immediately grafted, without delay, as shown by Stone and Zaur.[1e] Slow circulation had begun to appear in some of these eyes. It is obvious that the initial degenerative changes in the grafted eyes had progressed more rapidly after the delay in transplantation.

Within three months 3 eyes had slowly become resorbed until they were small corneoscleral sacs, 1 of which still showed a small amount of black pigment through a thickened, but clear, portion of the cornea. Three eyes at the end of fifty days gave an appearance similar to that of grafted eyes shown by Stone and Zaur [1e] thirty to forty days after operation, indicating that the recovery of these eyes was retarded about two weeks, as compared with eyes transplanted without delay. In about three months these eyes had regained their normal appearance except for a reduction in size. At this time the normal (left) control eye was removed, and return of vision in the grafts was proved by the methods described previously (Stone and Zaur [1e]).

The gross appearance of these eyes is indicated in a photograph (fig. *2*) taken one hundred and two days after operation. The appearance of the regenerated retina and its similarity to the normal (*4*) are shown in *5* of the figure. It is therefore obvious that some eyes can be kept as long as two days at a temperature of 8 C. and be successfully grafted.

Delay Three Days; Temperature 4 to 6 C. and 8 C.—In 5 cases right eyes were refrigerated for three days at a temperature of 8 C. before they were grafted. At this time the eyes were still clear, but the luster and color of the iris were not so brilliant as at the time of excision. Nine days after transplantation the cornea in all the grafts was becoming cloudy. The iris had darkened in most grafts, indicating rapid changes in the eyes. In fifty days 3 eyes had become small, darkly pigmented spheres with slightly cloudy corneas. Two other eyes at this time had not degenerated to the same degree. The corneas were clear. However,

the eyes slowly degenerated to small sacs by the end of four months. The other 3 eyes had reached this stage by the end of the third month. Therefore none recovered which had been refrigerated at 8 C. for three days.

In 5 other cases the eyes were kept for three days at a lower temperature, approximately 4 to 6 C. At the time they were grafted their gross appearance was about the same as that of the eyes which had remained for three days at a temperature of 8 C. At the end of ten days after transplantation the cornea was clear in all eyes and slow circulation was observed. In forty days the recovery of 2 grafts appeared similar to that of eyes which have been transplanted immediately after enucleation (Stone and Zaur [1c]). The other 3 grafts were smaller and gave the appearance of slower recovery. Unfortunately, 2 of the hosts escaped twenty-two days later, before the eyes had fully recovered for visual tests. The 3 surviving hosts showed large, normal-appearing eyes. One of the eyes, the slowest to recover, was about four fifths of the normal size. The normal (left) control eyes of these hosts were removed at this time, and visual tests showed that normal function had returned in the 3 cases. Two animals were killed one hundred and eight days after operation, and the appearance of the retina is indicated in *6*. Therefore a delay of three days before transplantation demands a temperature below 8 C. (about 4 to 6 C.) to bring about a successful result.

Delay Four Days; Temperature 0 C., 4 to 6 C. and 8 C.—Five right eyes were refrigerated four days at a temperature of 8 C. At the time they were grafted the yellow pigment in the iris was pale. The corneas and lenses were clear. The bulbs were not so firm as at the time of excision. At the end of a week after transplantation there were varying degrees of cloudiness in the corneas. In 2 cases the iris had sunken inward over a cloudy lens. In only 1 case did red spots in the iris indicate living red blood cells in loops of blood vessels. No circulation was observed. By the forty-fifth day 3 grafts were small, round, opaque, pigmented balls. Two eyes at this time were not so extensively degenerated. The corneas were clear. The iris was darkly pigmented and sunken. In three months 4 specimens were small white spheres with indications of varying amounts of centrally placed black pigment. One of the eyes was small with a thick, semitransparent cornea, through which one could see a black pigmented membrane with a large central opening. There was some golden pigment in the ventral portion of this iris. Since one could see a nonpigmented, pinkish background through the central opening, it was evident that the retinal area was permanently lost. Twenty-two days later this eye was almost completely resorbed.

In 2 cases a right and a left eye were left for four days at freezing temperature (0 C.). They were thawed in Ringer solution before graft-

ing. At this time the cornea and lens were clear. The iris was pale and sunken, and the pupil was distorted. These eyes never recovered but were rapidly resorbed, until by two months they were mere small white corneoscleral sacs.

In another group 5 right and 5 left eyes were excised, washed in sterile Ringer solution in the usual manner and, under sterile conditions, placed under refrigeration at a temperature of from 4 to 6 C. During the second day the thermal control to the ice box had failed to function for several hours before the trouble was discovered. At this time the temperature of the compartment in which the eyes were kept had risen above 10 C. The eyes were removed and placed under new sterile conditions, and the desired temperature was soon reinstated for the remainder of the four day period.

At the time the eyes were grafted 3 left eyes were discarded, since they were soft and partially collapsed. The remaining 7 were transplanted, although some of them appeared less firm and all were subnormal in appearance. All but 1 of these eyes were slowly being reduced to small sacs during the first month. In the exceptional case, although the graft gradually became smaller, it was on the sixty-ninth day, at the time of fixation, a small eye with a thickened, clear cornea, through which one could see black and yellow iris pigment, not arranged in the normal pattern which is so common in a fully recovered grafted eye. The pupil was maximally contracted. Circulation was rapid in the blood vessels of the iris. Histologically, the appearance of the eye was similar to that shown in *7* of the figure. The case was one of an eye undergoing slow resorption without sufficient surviving cells to insure its full recovery. In the light of other experiments later reported in this paper, it is obvious that the temporary rise in temperature above the intended refrigeration level of 4 to 6 C. accounted largely for the end results in this group of grafts.

Delay Five and Six Days; Temperature 4 to 6 C. and 8 C.—At the temperature of 8 C. 6 eyes were kept for five days and 5 eyes for six days before they were grafted. After refrigeration the eyes appeared soft. The iris was less brilliant, and occasionally loose pigment cells were seen between the cornea and the iris. At the end of a week after transplantation 3 of the eyes refrigerated for five days showed areas of the cornea sloughing. All of the eyes refrigerated for six days showed the same condition at this time. These eyes rapidly collapsed, and what remained was resorbed during the first month. The 3 eyes kept for five days which did not collapse during the first two weeks after transplantation were resorbed less rapidly, for at the end of a month they were small corneoscleral sacs, some of which contained small amounts of pigment.

In another group, 6 left eyes were kept for six days at a lower temperature (4 to 6 C.) before they were grafted. At the time the eyes of this group were transplanted they showed less damage than the eyes kept for five and six days at the higher temperature (8 C.). All these eyes healed and recovered circulation. At eighteen days 2 of them were reduced to one-half their original size, and by the end of a month they were small, flattened, pigmented sacs, being rapidly resorbed. Histologic examination of 1 of them showed a small corneoscleral sac filled with a mass of pigment and scattered groups of iris cells which had survived. The remaining 4 grafts were being resorbed at a much slower rate. Two of them were preserved for histologic study on the thirty-fifth day. Both were small eyes with thick corneas. In 1 eye the retina, which had attempted regeneration, was an uneven, solid wall of undifferentiated cells and with the slender iris formed a small cup surrounded by heavy choroid pigment. A small lentoid mass was embedded in the dorsal portion of the iris. In the center was a small spherical remnant of the original lens not yet completely degenerated. It was surrounded by a film of pigment cells. The other eye showed a better attempt at regeneration, although it was also very small. The retina was thicker, and limited regions showed differentiation of retinal layers. The original lens had completely disappeared, and a new but small one had regenerated from the dorsal part of the iris, similar to the lens shown in *7*. There was no attempt to form an optic nerve in either case.

The 2 remaining eyes were kept under observation for sixty-four days because at the end of the first month there was indication these eyes might make a good attempt at recovery. However, at the end of two months 1 eye became rather small. The condition is shown in *7* and is typical of an eye undergoing slow resorption in which a portion of the retina had attempted regeneration. A small lens had also regenerated from the dorsal pupillary margin of the iris. The larger of the 2 eyes possessed a new lens of greater size. Much of the retina had reached a considerable degree of regeneration and differentiation. The central part was greatly retarded, owing to a rupture in the wall of the eyeball.

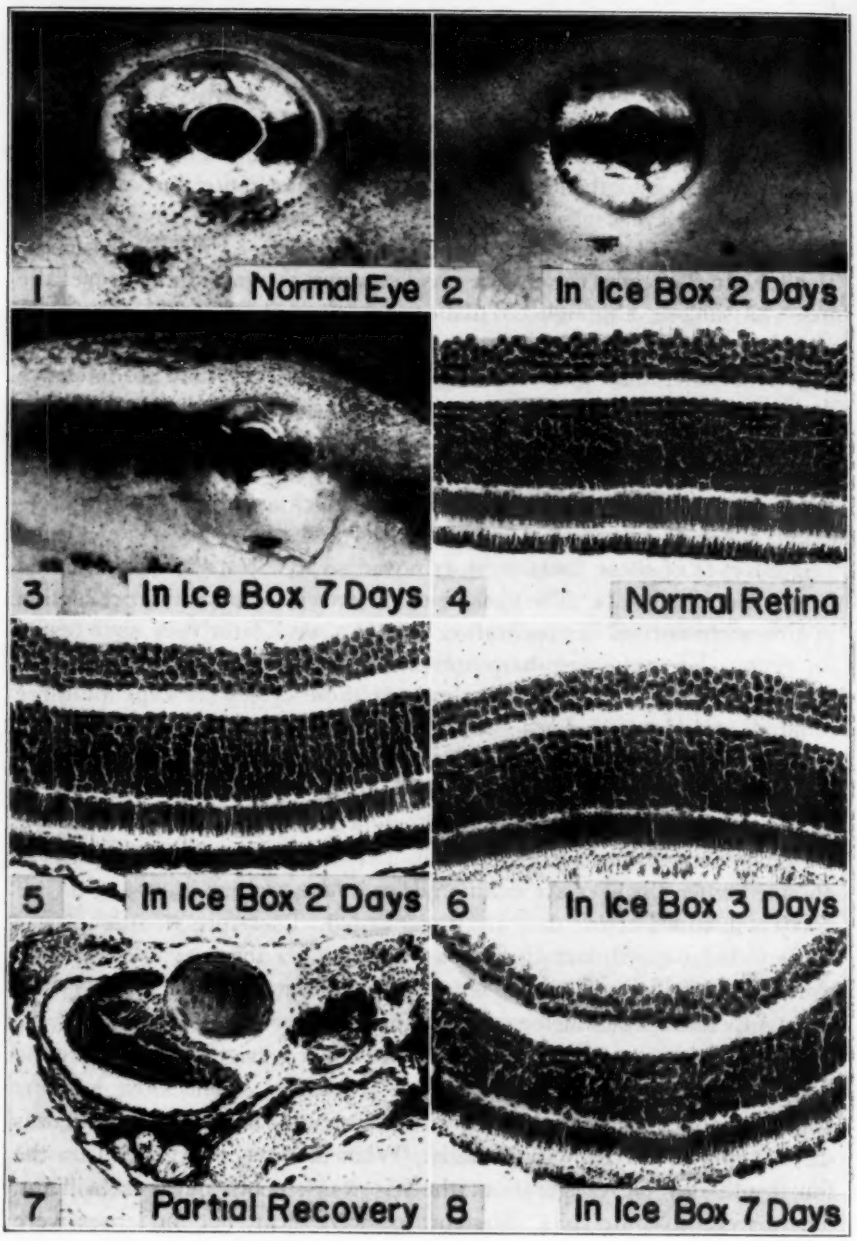
Delay Seven to Fourteen Days; Temperature 0 C., 4 to 6 C. and 8 C. —Eight eyes were kept for seven days and 2 eyes for eight days at freezing temperature. At the time they were grafted most of them were clear and in good condition. Only 1 eye had a slightly opaque lens and cornea. The gross appearance was deceiving, for by the end of a week most of the grafts were rapidly degenerating. In some eyes portions of the cornea and iris were sloughing. Although 2 eyes were kept over two months, because the corneas remained clear for a long period, there was no ability in any of these eyes to combat the steady degeneration which overtook them.

Since better results were obtained when eyes were kept at a temperature of from 4 to 6 C., an attempt was made to refrigerate 6 left eyes for a period of seven days at that temperature before they were grafted. When they were taken from the ice box, the corneas and lenses in all cases were clear. Two eyes showed a yellow fringe of iris cells, which had wandered inward from the pupillary margin. A brownian movement of pigment granules indicated that some cells had disintegrated. All other eyes showed a smooth, bright, clear iris, with not quite the same luster as the normal eye.

By the twenty-fourth day after transplantation 4 grafts had become smaller. In 2 of them the cornea was becoming opaque. In all 4 eyes the iris was sunken, although circulation was present. These 4 eyes were undergoing resorption. In 2 other grafts, however, the eyes were only slightly smaller than normal and gave good evidence that no extensive degeneration was taking place, as in the 4 grafts just mentioned.

At the end of seventy-one days the pigment pattern was returning in the iris of these eyes. A new lens was regenerating. The grafts were recovering, but at a slower rate than eyes which are transplanted immediately after enucleation. At one hundred and twelve days the normal (right) eyes of these hosts were removed so that tests for vision could be made on the grafts. The eyes, with the exception of a slight reduction in size, were normal in appearance. About a week later they were tested for vision. Vigorous and sharp normal visual responses to a moving lure were clearly demonstrated. The hosts of these eyes were kept for three hundred and sixty-six days. At the end of this time the grafts were still large, beautiful, normal-functioning eyes. A motion picture record was made of 1 of these eyes. Its appearance at this time is shown in *3* of the figure. The regenerated retina is also shown in *8*.

It appears from these experiments that the best survival of grafts is obtained when the eyes are maintained at a temperature from 4 to 6 C. if delay is intended before they are transplanted. Therefore an attempt was made to delay transplantation for a period longer than seven days when eyes were refrigerated at this temperature. Four left eyes were kept at this temperature for fourteen days before they were grafted. They were briefly examined at various periods while under refrigeration. After the first week in the ice box epithelial cells tended to scale loose in some places on the surface of the cornea. After eight to ten days the lenses did not appear as clear as formerly. When the eye was grafted on the fourteenth day of refrigeration, the iris was smooth but less brilliant. There were no loose cells. The corneas were clear, but the lenses were slightly opaque. The eyes were soft, and 1 was broken in an attempt to graft it. After two days 1 eye was clear. The cornea in another eye was rather opaque. Two eyes had sloughed and broken down completely.


1 Normal Eye
2 In Ice Box 2 Days
3 In Ice Box 7 Days
4 Normal Retina
5 In Ice Box 2 Days
6 In Ice Box 3 Days
7 Partial Recovery
8 In Ice Box 7 Days

(See legend on opposite page)

The 2 eyes which did not disintegrate early were small, opaque corneoscleral sacs in twenty-one days, showing a rapid resorption of the degenerating tissue of the eye. Histologically examination of 1 of them revealed an extensive invasion of blood vessels among scattered clumps of pigment and isolated fragments of the iris.

CONCLUSIONS AND SUMMARY

From the results of these experiments it is clear that a period of refrigeration for the isolated adult eye of this species much longer than seven days does not preserve the eye sufficiently for successful transplantation. Perhaps with a great many experiments it might be shown that the time could be extended a day or two in obtaining a successful result. It is not unexpected that the cornea has considerable survival capacity and may remain clear for a long time. This is expressed somewhat for vertebrates in general by the fact that corneal banks are now established for transplants in human eyes. However, considering the fact that when the adult eye of this salamander is transplanted a new lens regenerates from the dorsal pupillary margin of the iris and a new retina regenerates from the undegenerated ciliary margin of the old retina, it is remarkable that cells which replace these highly differentiated parts of the eye can survive so well for as long as seven days under refrigeration.

These experiments can be summarized in the following statements:

Seventy enucleated eyes of the adult salamander (the common vermilion spotted newt, Triturus viridescens) were refrigerated at a tem-

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EXPLANATION OF PLATE.

1, normal adult eye of Triturus viridescens; × 8.

2, eye one hundred and two days after transplantation; × 8. Refrigeration at a temperature of 8 C. was maintained for two days. Visual function was demonstrated.

3, eye three hundred and sixty-six days after transplantation; × 8. Refrigeration at a temperature of 4 to 6 C. was continued for seven days. Visual function was demonstrated one hundred and nineteen days after transplantation.

4, photomicrograph of a section of the normal retina of the adult eye of Triturus viridescens; × 130.

5, photomicrograph of a section of the retina of a functional eye one hundred and two days after transplantation; × 130. Refrigeration had been continued for two days at a temperature of 8 C.

6, photomicrograph of a section of the retina of a functional eye one hundred and four days after transplantation; × 130. Refrigeration had been continued for three days at a temperature of 4 to 6 C.

7, photomicrograph of a section of a partially resorbed eye sixty-four days after transplantation; × 65. Limited regeneration of the retina and lens is indicated. Refrigeration had been continued for six days at a temperature of from 4 to 6 C.

8, photomicrograph of a section of the retina of a functional eye (that shown in *3*) three hundred and sixty-six days after transplantation; × 130. Refrigeration had been continued for seven days at a temperature of from 4 to 6 C.

perature of from 0 to 8 C. in sterile Ringer solution for periods ranging from two to fourteen days and were then transplanted into freshly denuded orbits of new hosts. Right and left eyes were grafted and normally oriented.

When the eyes were kept under freezing conditions (0 C.), the grafts eventually degenerated, the rapidity with which they succumbed depending partially on the time they had remained under refrigeration.

After two days of refrigeration at 8 C. the success of the grafts is expressed by the fact that in some cases the eye eventually became a normal-appearing normally functioning organ again.

Refrigeration for longer than two days required a lower temperature (4 to 6 C.) to insure survival of the graft and successful transplantation. Eyes isolated as long as seven days at this temperature were successfully grafted, and return of vision was demonstrated a little over three months after they were transplanted. These eyes remained functional and were normal in appearance one year after they were grafted. At this time the hosts were killed for microscopic studies. A motion picture record was obtained of these experiments.

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OCULAR DERMATITIS FROM LOCAL PENICILLIN

Report of Two Cases

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SINCE the clinical introduction of penicillin by Abraham and associates [1] for the treatment of systemic and local infections, the serious toxic manifestations of this drug have been remarkably few. Keefer and associates [2] encountered relatively mild untoward reactions in 69 (13.8 per cent) of their series of 500 patients treated systemically with penicillin. Of this group, urticaria occurred in 14 patients, chills and fever in 17 and localized thrombophlebitis in 19. All the reactions were transitory and did not require cessation of the drug therapy. Sensitivity to penicillin was not evident, even though several patients had repeated prolonged courses. Lyons [3] reported that urticaria was the most common complication in his group, occurring in 5.7 per cent of the 209 patients treated systemically with penicillin. He attributed these reactions to toxic impurities rather than to the active penicillin fraction. He found that thrombophlebitis, which often occurred at the site of the intravenous injection, could be avoided by frequent change in the position of the needle. Herrell and associates [4] noted 2 cases of cutaneous sensitivity in their series of 150 patients treated parenterally with penicillin. They cautioned against the continued use of this drug in the presence of a generalized cutaneous reaction because of the possibility of development of exfoliative dermatitis.

The ready diffusibility of penicillin and its remarkable bacteriostatic power against sensitive staphylococci and streptococci, even in the presence of purulent secretion, are rapidly establishing this drug as a most effective therapeutic agent in the local treatment of external ocular

1. Abraham, E. P.; Chain, E.; Fletcher, C. M.; Gardner, A. D.; Heatler, N. G.; Hennings, M. A., and Florey, H. W: Further Observations on Penicillin, Lancet **2**:177 (Aug 16) 1941.

2. Keefer, C. S.; Blake, F. G.; Marshall, E. K., Jr.; Lockwood, J. S., and Wood, W. B., Jr.: Penicillin in the Treatment of Infections: A Report of Five Hundred Cases, J A. M. A. **122**:1217 (Aug. 28) 1943.

3. Lyons, C.: Penicillin Therapy of Surgical Infections in the U. S. Army: A Report, J. A. M. A. **123**:1007 (Dec. 18) 1943.

4. Herrell, W. A.; Nichols, D. R., and Hillman, D. H.: Penicillin, J. A. M. A. **125**:1003 (Aug. 12) 1944.

diseases. Despite the recent great increase in the clinical use of penicillin for this purpose, reports regarding its hypersensitive reactions have thus far been meager. Florey and Florey [5] noted no toxic effects in local treatment of 172 patients with penicillin, 89 of them having ocular infections. The drug was instilled at frequent intervals in a petrolatum ointment or in distilled water in a strength of 400 to 800 Oxford units per gram or cubic centimeter. Cashell [6] reported no untoward reactions in his series of 57 cases of infections of the eye treated locally with penicillin. Bellows,[7] on the other hand, noted 4 instances of ocular hypersensitization in 46 cases in which topical treatment with penicillin was employed. A severe ocular dermatitis, associated with fever and malaise, was reported by Keyes [8] after instillation of 4 drops of a saline solution of sodium penicillin containing 1,000 units per cubic centimeter in each eye. Pyle and Rattner [9] reported a case of contact dermatitis resulting from penicillin, with a positive reaction to the patch test. Further analysis of the drug proved that the pure penicillin, not the medium, produced the allergic reaction.

The following 2 cases of ocular dermatitis due to local application of penicillin are reported because of the apparent infrequency of the condition and for the purpose of stimulating further observation of such reactions. They occurred in a series of 52 cases of external infections of the eye treated at this clinic with sodium penicillin in saline solution or ointment, the strength varying from 500 to 3,000 Oxford units per cubic centimeter or gram. The results of this study will be reported subsequently.

REPORT OF CASES

CASE 1.—A soldier aged 25 was admitted to the hospital on Jan. 15, 1945 because of redness and irritation of both eyes, which he had noticed during the past two months. Treatment of this condition at a local dispensary had produced no appreciable improvement. His left eye had been practically blind since the age of 3, the loss of vision following a severe ulceration of the cornea.

Physical examination revealed an essentially normal condition except for his eyes. Vision was 20/20 in the right eye and was limited to ability to count

5. Florey, M. E., and Florey, H. W.: General and Local Administration of Penicillin, Lancet **1**:387 (March 27) 1943.

6. Cashell, G. T. W.: Treatment of Ocular Infections with Penicillin, Brit. M. J. **1**:420 (March 25) 1944.

7. Bellows, J. G.: Penicillin Therapy in Ocular Infections, Am. J. Ophth. **27**:1206 (Nov.) 1944.

8. Keyes, J. E. L.: Penicillin in Ophthalmology, J. A. M. A. **126**:610 (Nov. 4) 1944.

9. Pyle, H. D., and Rattner, H.: Contact Dermatitis from Penicillin, J. A. M. A. **125**:903 (July 29) 1944.

fingers at 1 foot (30 cm.) in the left eye. A moderate injection of the conjunctiva was present in both eyes, being especially noticeable in the lower palpebral portions. This was associated with mild crusting blepharitis. The entire pupillary portion of the left cornea was densely scarred throughout its substance and contained deep vascularization. Neither cornea stained with fluorescein. A smear of material from the conjunctiva showed no organisms. A culture of the conjunctival secretion, however, revealed colonies of the beta hemolytic streptococcus.

Treatment with penicillin, in a strength of 1,500 Oxford units dissolved in each cubic centimeter of isotonic solution of sodium chloride, was begun January 19. Two drops of this solution was instilled in each conjunctival sac every two hours during the waking portion of the day. Penicillin of similar strength was also applied to the eyes in a modified white ointment U. S. P.[10] each evening before retiring. A favorable therapeutic response was noted after six days of this regimen, at which time no organisms could be found on culture. The penicillin drops were then instilled at intervals of four hours. On January 27 a mild dermatitis of the eyelids was noted, associated with a slight injection of the conjunctiva. All penicillin therapy was stopped, and the reaction subsided on

Fig. 1 (case 1).—Ocular dermatitis, showing acute allergic reaction to penicillin.

the following day. Treatment with penicillin was resumed on January 29, and after the third instillation a severe ocular dermatitis of both eyes rapidly appeared (fig. 1). The clinical picture closely resembled an acute dermatitis due to atropine. All the eyelids were extremely red and edematous, and their skin was eczematous and weeping, especially of the lower lids. The bulbar and palpebral conjunctiva of both eyes was congested, and a seromucoid secretion was evident along the margins of the lower lids.

After the prompt cessation of penicillin therapy, the acute allergic reaction gradually subsided, disappearing in four days. Marked scaliness of the skin of the lids, however, appeared at this time, associated with moderate wrinkling and itching, which persisted till February 8, a period of five days. After the complete disappearance of the ocular dermatitis, a provocative test with 1 drop of penicillin in saline solution in a strength of 250 units per cubic centimeter promptly produced the reappearance of symptoms, though less severe, when instilled into the eye. No history of allergy could be elicited from the patient.

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10. White wax, 3 per cent; hydrous wool fat, 8 per cent, and petrolatum, 89 per cent.

The patch test gave a negative reaction for penicillin. The cutaneous reaction, however, was strongly positive for the drug.

The patient was returned to light duty and was cautioned to avoid penicillin therapy in the future.

CASE 2.—A soldier aged 36 was referred to the eye clinic of the station hospital on Feb. 5, 1945 as an outpatient because of redness and discomfort which had been present in both eyes during the past five days. Vision was 20/20 in each eye. Ophthalmic examination revealed evidence of acute bilateral conjunctivitis. The cornea did not stain with fluorescein. A conjunctival smear revealed no organisms. Culture of the conjunctival secretion, however, revealed a beta hemolytic streptococcus.

The following morning the patient was issued a saline solution of penicillin containing 2,000 units per cubic centimeter and was advised to instil 2 drops in each eye every two hours of the waking day. The solution was to be kept in the

Fig. 2 (case 2).—Ocular dermatitis from the use of penicillin, involving the lower lids and the cheeks.

refrigerator when not in use. A pronounced improvement was noted seventy-two hours later, both subjectively and objectively. No organisms were obtained from culture at that time. On February 10, after he had used penicillin four days, a small red, vesicular area of dermatitis was noted on the right lower lid and the upper portion of the face. This lesion spread during the next twenty-four hours over the bridge of the nose, similarly involving the left side of the face and the lower lid and assuming the shape of a butterfly (fig. 2). The conjunctiva was not involved. The reactions of both the patch and the cutaneous tests were positive for penicillin. The dermatitis gradually resolved and completely disappeared five days after cessation of use of the drug.

COMMENT AND SUMMARY

Two cases of ocular dermatitis due to local instillation of penicillin are described. In the first case the condition resembled acute dermatitis due to atropine, while in the second case it simulated contact dermatitis. The allergic reactions gradually subsided with cessation of treatment with the drug.

As local application penicillin becomes more general in treatment of external diseases of the eye, hypersensitive reactions of this type assume greater clinical significance. The spectacular results frequently obtained with this drug in such cases may be tempered by the allergic manifestations of susceptible persons. In view of this possibility, further observation is necessary to determine whether this form of penicillin therapy should be limited to the external ocular infections which have resisted ordinary therapeutic measures. In these instances, preliminary patch and cutaneous tests of the drug may be advisable, in addition to culturing the organism and determining its sensitivity.

The relationship between these topical allergic phenomena and the systemic reactions due to penicillin given parenterally requires further clinical and experimental investigation for proper evaluation.

CONGENITAL MALFORMATIONS INDUCED IN RATS BY MATERNAL VITAMIN A DEFICIENCY

I. Defects of the Eye

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AND
ELIZABETH SCHRAFFENBERGER, A.B.
CINCINNATI

ALTHOUGH congenital blindness of the offspring of poorly nourished animals has often been described, the early reports were specific neither in the analysis of the nutritional deficiency nor in the description of the ocular defects. Most of the observations were made on cattle, and Moore, Huffman and Duncan [1] have reviewed the literature pertaining to this field. Two types of congenital blindness can be distinguished: "the true vitamin A type," which is obviously a severe form of xerophthalmia,[2] and another type which is associated with constriction of the optic foramen.[3] The latter, characterized by a dilated pupil and absence of inflammation of the external structures of the eye, is due to atrophy of the optic nerve caused by its passage through the optic foramen, apparently because of bony pressure.[1] It was difficult to attribute this congenital ocular defect to maternal vitamin A deficiency until Wolbach and Bessey [4] demonstrated that the neural lesions of vitamin A deficiency are caused by a disproportionate growth of the central nervous system in relation to the surrounding bone. Constric-

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From the Children's Hospital Research Foundation, Department of Pediatrics, University of Cincinnati College of Medicine.

1. Moore, L. A.; Huffman, C. F., and Duncan, C. W.: J. Nutrition **9**:533, 1935.

2. (*a*) Mason, K. E.: Am. J. Anat. **57**:303, 1935. (*b*) Hart, G. H., and Guilbert, H. R.: Bulletin 560, California Agricultural Experiment Station, 1933, p. 3. (*c*) Jones, I. R.; Eckles, C. H., and Palmer, L. S.: J. Dairy Sc. **9**:119, 1926. (*d*) Mead, S. W., and Regan, W. M.: ibid. **14**:283,1931.

3. Crocker, W. J.: Cornell Vet. **9**:171, 1919. Reed, O. E.; Huffman, C. F., and Addington, L. H.: J. Dairy Sc. **11**:488, 1928. Halverson, J. O., and Sherwood, F. W.: Technical Bulletin 39, North Carolina Agricultural Experiment Station, 1930, p. 5. Converse, H. T., and Meigs, E. B.: Proc. Am. Soc. Animal Production **24**:141, 1932. Datta, S. C. A.: Indian J. Vet. Sc. **3**:254, 1933. Moore, L. A.: J. Nutrition **17**:443, 1939; J. Dairy Sc. **22**:803, 1939.

4. Wolbach, S. B., and Bessey, O. A.: Vitamin A Deficiency and the Nervous System, Arch. Path. **32**:689 (Nov.) 1941.

tion of the optic foramen can now be considered a "true" manifestation of vitamin A deficiency. Davis and Madsen [5] made quantitative studies of carotene intake of cattle and of plasma levels of carotene and vitamin A during pregnancy in heifers who gave birth to weak and blind calves. They found that heifers receiving 30 and 45 micrograms of carotene remained apparently normal but gave birth to defective calves.

The manifestations of prenatal vitamin A deficiency in pigs described by Hale [6] were of an entirely different character. This investigator fed gilts of known stocks a diet deficient in vitamin A and possibly in other nutritional factors. Owing to anophthalmos or microphthalmos, the offspring were blind. They also showed other malformations, such as accessory ears, cleft palate and harelip, subcutaneous cysts and misplaced kidneys. Hale proved the nutritional origin of these malformations by preventing them when the experimental diet was supplemented with cod liver oil or green fodder. He also proved that genetic factors could be ruled out as the cause of the malformations, since matings of abnormal sons to their mothers or of abnormal brothers to their abnormal sisters resulted in normal offspring if the females were fed an adequate diet during pregnancy.

Reproduction on diets deficient in vitamin A has been thoroughly studied in the rat,[7] particularly by Mason,[2a] who described fetal death, prolonged gestation and difficult parturition but not congenital malformations of the offspring. Cannon [8] attempted to induce malformations in the offspring of female rats which were depleted in vitamin A. He observed sterility, premature resorption of the fetuses, stillbirths and prolonged gestation. However, no congenital malformations were induced.

In 1944 we [9] reported the appearance of congenital malformations in the offspring of female rats that were depleted of vitamin A. The depletion of the mothers was achieved by placing female rats of the Sprague-Dawley strain for approximately three months after weaning on a preparatory diet (diet U) which had the following percentage

5. Davis, R. E., and Madsen, L. L.: J. Nutrition **21**:135, 1941.

6. Hale, F.: J. Hered. **24**:105, 1933; Am. J. Ophth. **18**:1087, 1935; Texas State J. Med. **33**:228, 1937.

7. Evans, H. M., and Bishop, K. S.: Anat. Rec. **23**:17, 1922. Evans, H. M.: J. Biol. Chem. **77**:65, 1928. Sherman, H. C., and MacLeod, F. L.: J. Am. Chem. Soc. **47**:1658, 1925. Tansley, K.: Biochem. J. **30**:839, 1936. Newton, W. H.: J. Physiol. **92**:32, 1938.

8. Cannon, M. D.: Proc. Soc. Exper. Biol. & Med. **44**:129, 1940.

9. Warkany, J., and Schraffenberger, E.: Proc. Soc. Exper. Biol. & Med. **57**:49, 1944.

composition: ground whole wheat, 74; crude casein (Casein Company of America), 15; brewers' yeast (Mead Johnson and Company), 10; sodium chloride C. P., 1. This diet was supplemented with 60 U. S. P. units of vitamin D (Drisdol, Winthrop Chemical Company) and 4 micrograms of carotene (S. M. A. Corporation) in cottonseed oil every tenth day. The small amount of carotene was added to allow growth and maturation to proceed, without storage of vitamin A. During this preparatory period about 10 Gm. of frozen ground horse muscle without bones was given weekly to each rat to promote growth.

When the female rats reached a weight of 150 to 160 Gm. and regular estrus cycles were established, they were placed on the purified diet (diet W) and bred immediately to males of the same strain which had been reared on an adequate diet.

The purified diet (diet W), which was completely free of vitamin A, had the following percentage composition: sucrose, 68; vitamin test casein, 18; vegetable oil, 10, and salt mixture 4[10]; 100 Gm. of this diet was supplemented with 0.8 mg. of thiamine hydrochloride, 0.8 mg. of pyridoxine hydrochloride, 0.8 mg. of riboflavin, 1 mg. of calcium pantothenate, 10 mg. of nicotinamide and 100 mg. of choline chloride. Every tenth day preparations of vitamin D (1 drop of a 1:4 dilution of Drisdol in olive oil), vitamin E (1 drop of a solution of 5 Gm. of alphatocopherol in 100 cc. of olive oil) and a vitamin K analogue (1 drop of a solution of 1 mg. of menadione in 5 cc. of olive oil) were also given.

A daily vaginal smear was made from each mature female in order to confirm breeding by the finding of sperm and to watch for signs of beginning resorption. Loss of weight and profuse vaginal bleeding were considered to mean interruption of pregnancy. The profuse bleeding of resorption must be distinguished from the normal blood sign, which appears between the tenth and the fifteenth day and which consists of a small amount of blood in the vaginal smear. In case of interruption of pregnancy the animals were opened and the fetuses removed and examined. When the young were carried to term, the mothers were opened on the twenty-second day of gestation. No attempt was made to keep alive the young thus removed.

One hundred and forty females were raised and bred in this manner, and in 96 of them sperm were found. Neither fetuses nor young were obtained from 60 females which died before the fourteenth day of gestation or resorbed their embryos completely. Litters of 29 females whose pregnancy was interrupted after the thirteenth day were examined. One litter was removed on the thirteenth day (8 fetuses), 2 on the fourteenth day (16 fetuses), 7 on the fifteenth day (54 fetuses), 11 on

10. Hubbell, R. B.; Mendel, L. B., and Wakeman, A. J.: J. Nutrition **14**:273, 1937.

the sixteenth day (68 fetuses), 5 on the seventeenth day (14 fetuses), 1 on the eighteenth day (7 fetuses), 1 on the nineteenth day (9 fetuses) and 1 on the twentieth day (2 fetuses). Seven mothers carried their young to term. Thirty-nine mature young were obtained from them. Twenty-one of these were born alive, and 18 were stillborn.

Fig. 1.—Abnormal "open eye" in a newborn rat.

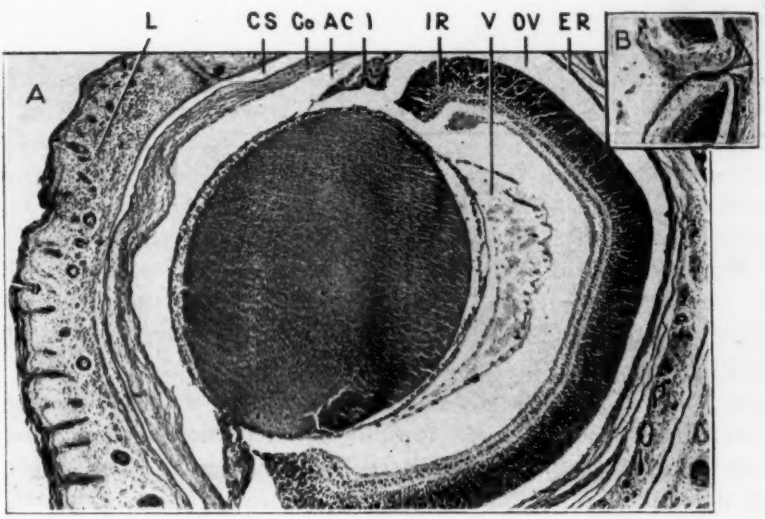

Fig. 2.—*A*, section of the eye of a normal newborn rat (approximately × 33). In this figure, and in figure 4, *L* indicates lower lid; *CS*, conjunctival space; *Co*, cornea; *AC*, anterior chamber; *I*, iris; *IR*, internal leaf of retina; *V*, vitreous; *OV*, space of optic vesicle; *ER*, external leaf of retina.

B, region of the optic nerve of the same eye (approximately × 33).

Twenty-five of the young born at term showed an external abnormality of the eye. In place of the closed eye of the normal newborn

rat "open eyes" (fig. 1) were seen. This open eye, which showed sometimes a red discoloration between the rudimentary lids, was present bilaterally in 22 young and unilaterally in 3 young. Serial sections were made of the heads of 16 of these young. Some of them had open eyes, and in others the eyes appeared externally normal. However, all the eyes sectioned proved abnormal on histologic examination. The degree of abnormality varied, but a fibrous retrolenticular membrane containing the vascular network of the hyaloid artery was seen in all the eyes examined.

The long axis of the eye of the newborn rat deviates from the sagittal plane, since its anterior end points anterolaterally. In spite of this deviation, in the following description the region of the anterior pole of the eyeball will be called "anterior" and that of the posterior pole "posterior," although "anterolateral" and "posteromedial" would be more correct. The sections were made in the frontal plane, proceeding in a ventrodorsal direction from the nostrils to the pharynx.

Three representative sections of an abnormal eye will be described in the following paragraphs.

Figure 3 illustrates a ventral section through the right eye of an abnormal newborn rat, which showed externally a definite red discoloration in the region of the eyes. Superficial comparison with figure 2*A*, a ventral section through the eye of a normal newborn rat, discloses a number of defects in the abnormal eye. In the anterior portion is found almost complete obliteration of the lower conjunctival sac and of the intraocular chambers. No traces of the upper conjunctival sac can be seen. Behind the point of junction of the upper and lower lids, the sclera and the external leaf of the retina are recognizable. The space between the lower conjunctival sac and the lens is occupied by a dense tissue, which apparently represents the mesoderm, which in the normal eye contributes to the formation of the cornea and of the iris. The lens appears essentially normal. The margin of the optic cup extends forward well past the equator above and barely reaches the equator below, so that the lower parts of the lens are in direct contact with mesodermal tissue. This defect in the lower portion of the cup represents the anterior portion of the persisting fetal fissure. The vitreous is not developed. The internal leaf of the retina is approximately of normal thickness but of completely abnormal structure. This will be described in detail later. The external leaf of the retina consists of a single layer of epithelial cells. The space between the two layers, the lumen of the optic vesicle, is filled with blood. The upper margin of the optic cup, which is placed in front of the equator of the lens, is formed by the junction of the outer and the inner leaf of the retina. The internal leaf decreases abruptly in height near the margin. The

angle between the external and the internal leaf is wide open, and its sides represent the rudiments of an iris.

In figure 4, which is a section approximately through the center of the eye, the lids appear to be closed, and a line of fusion is visible. This line of fusion traverses the lids in an oblique direction, and its cells are directly connected with those that fill out the conjunctival sac. The conjunctival space is not developed, since the palpebral and the

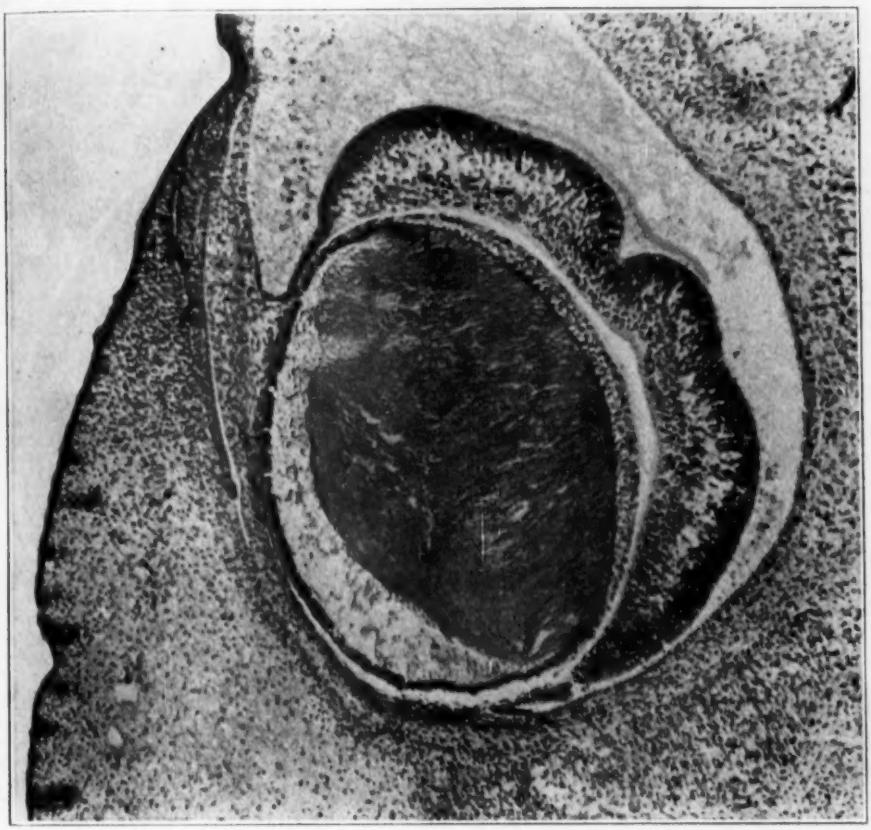

Fig. 3.—Section of the eye of an abnormal newborn rat, showing the lack of differentiation in the anterior parts of the eye (approximately × 80). The lower part of the optic cup does not enclose the lens.

bulbar conjunctival epithelium are in close contact. The bulbar epithelium adheres firmly to a mass of mesodermal tissue, which corresponds to the cornea and probably also to the stroma of the iris. This mesodermal tissue can be divided into a loosely woven anterior part and a dense posterior part. The dense portion is covered posteriorly by a complete row of epithelial cells, which is a direct continuation of

the external leaf of the retina. Thus, the anterior chamber, the iris, the ciliary body and the posterior chamber cannot be recognized as individual structures. Behind the epithelial cells of the external leaf a linear space is seen, which represents a part of the cavity of the optic vesicle. This space enlarges toward the upper part of the eye, where it becomes dome shaped. It forms only a narrow cleft in the lower

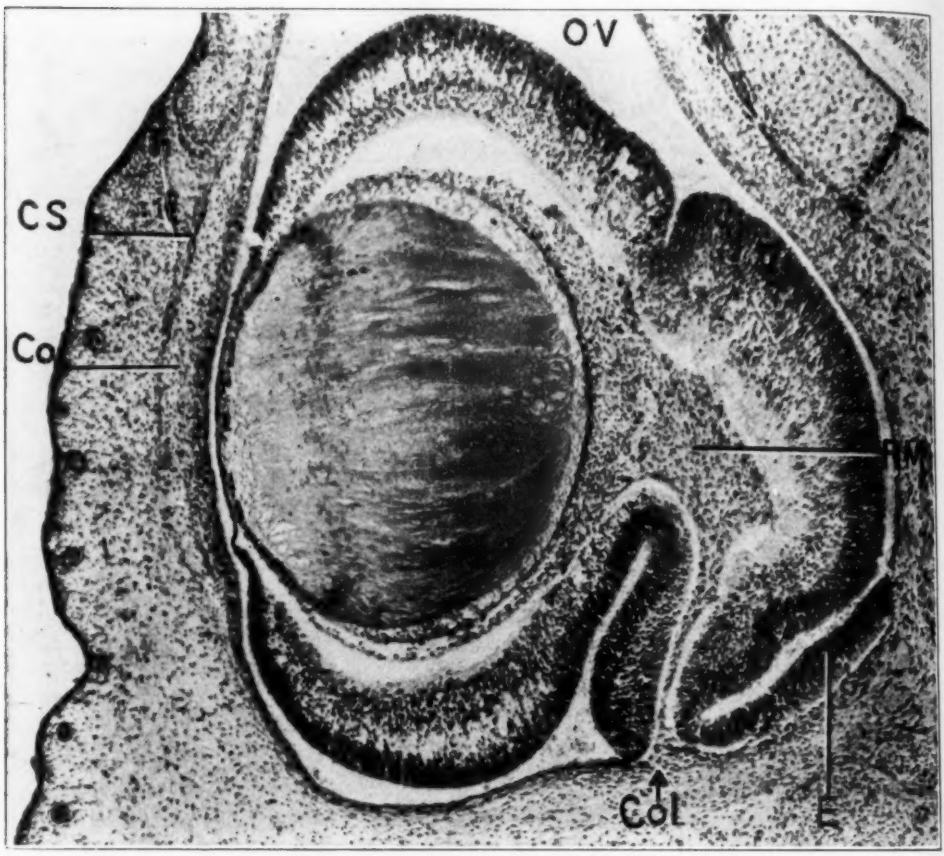

Fig. 4.—Section of the eye of an abnormal newborn rat, showing coloboma (*Col*), eversion of the retina (*E*) and fibrous retrolenticular membrane (*RM*) connected with extraocular mesoderm (approximately × 80).

and posterior portion of the eye. The internal leaf of the retina is of approximately normal thickness with the exception of the most anterior part, which forms a single layer in front of the lens. This layer corresponds to the pigment layer of the normal iris (pars iridica retinae). The lower and posterior part of the internal leaf of the retina is split by a strand of connective tissue which connects extraocular meso-

derm and the retrolenticular connective tissue replacing the vitreous humor. This fibrous tissue, which occupies the space of the vitreous, consists of a dense network of cells in which a number of capillaries can be discerned. The connective tissue cells immediately behind the lens have small, dark and oblong nuclei, the long axes of which run parallel with the posterior surface of the lens. The network of cells between the capillaries is somewhat looser, and larger, round nuclei which are poor in chromatin are interspersed with dark, small nuclei. There is no sharp borderline toward the layer of nerve fibers of the retina. The fibrous retrolenticular tissue decreases in thickness toward the equator of the lens, where it ends. The apparent split of the retina by mesodermal tissue represents an oblique section through the fetal fissure somewhat behind the equator of the eye. The internal leaf of the retina forms several folds and is distinctly everted behind the point where the retrolenticular and the extraocular mesoderm join. Thus, there is a duplication of the internal leaf of the retina, and the "innermost" layers of the everted portion are turned outward and face the choroidea. Posteriorly the everted retina ends abruptly; it diminishes in height at the point of junction with the external leaf of the retina, which consists of a single layer of cells. In the areas not folded the internal leaf of the retina is of normal thickness; it has differentiated into two ill defined layers of cells, separated by a loose network of fibrils. The denser outer layer consists of twelve to fifteen rows of cells with round, light nuclei. Within the loose cellular layer, a layer of nerve fibers can be seen.

Figure 5 represents a dorsal section through the right eye of another abnormal newborn rat near the optic nerve. The internal leaf of the retina is folded in many places and everted below and anterior to the retinal cleft. The center of the cleft is traversed by a thick strand of connective tissue which links extraocular mesoderm with the retrolenticular fibrous membrane. This strand is pierced in its entire length by a long and thin blood vessel, which is lined by a single layer of endothelial cells. In the retinal gap nerve fibers are seen on both sides of the mesodermal strand. In more dorsal sections this strand becomes thinner and more enclosed in nerve fibers.

The sections described illustrate some of the more obvious anomalies seen in the eyes of the young of mothers fed a diet deficient in vitamin A. In spite of variations in the individual eyes, certain features common to the majority of them can be discussed. The abnormalities of the lids vary greatly. Externally they may appear closed, although the line of fusion is abnormal. Their conjunctival surface is frequently closely attached to the corneal epithelium, since the conjunctival space does not develop. In "open eyes" the lids are not fused, and an

abnormal, fibrotic and often blood-tinged tissue is found in place of the cornea within the palpebral fissure. In case of absence of the anterior chamber a thick mesodermal membrane is seen between the lids, on one side, and the external leaf of the retina or the lens, on the other side. This membrane consists of the two layers of different texture. The anterior layer appears to correspond to the substantia propria of the cornea, and the denser posterior layer, to the stroma of the iris. The iris is present in a rudimentary form only. Its stroma

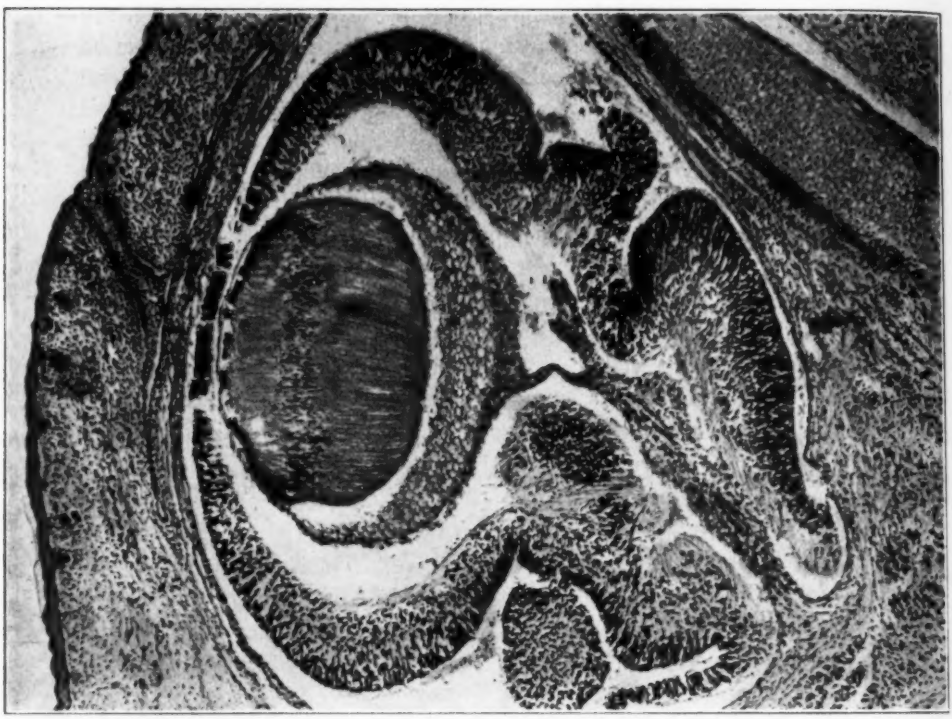

Fig. 5.—Section of the eye of an abnormal newborn rat near the optic nerve, showing coloboma, eversion of the retina and a fibrous band which links the retrolenticular membrane with extraocular mesoderm (approximately × 66).

is in the central ("pupillary") area closely connected with the anterior pole of the lens. In its peripheral parts it is covered posteriorly by the external leaf of the retina. The most anterior part of the internal leaf of the retina, which consists of a single layer of cells (fig. 3) and which corresponds to the pigment layer of the mature iris, is separated throughout from the external leaf by the lumen of the optic vesicle. Thus many features of the fetal rudiments of the iris are maintained in these abnormal eyes of young born at term.

Extensive changes are found in the lower parts of the optic cup. These areas, which are phylogenetically and ontogenetically the youngest parts of the eye, are particularly susceptible to modification and mutation.[11] The first section described (fig. 3) shows the optic cup open anteriorly in its lower part. While the cup encloses completely the upper half of the lens, the failure of the fetal fissure to fuse in this region makes it appear as though the lower half is not encased in the ectodermal parts of the eye but rests directly on mesoderm. The second

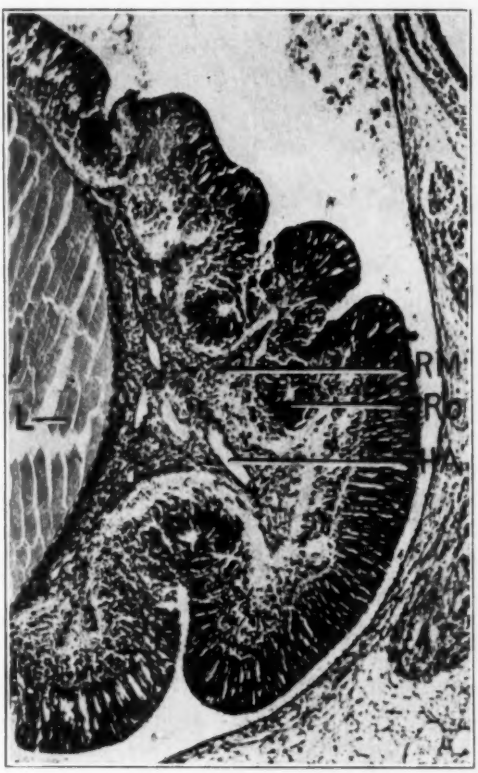

Fig. 6.—Section through posterior portion of an abnormal eye. *L* indicates the lens; *RM*, the retrolenticular membrane; *Ro*, rosette; *HA*, branch of hyaloid artery (approximately × 70).

section (fig. 4) illustrates a gap in the lower part of the optic cup and eversion of the retina posterior to it. The gap is traversed by a strand of mesodermal tissue. The third section (fig. 5) shows also a retinal cleft with retinal eversion near the optic nerve. Within the fibers of the optic nerve a thick band of mesodermal tissue is seen, which

11. Mann, I. C.: Developmental Abnormalities of the Eye, Cambridge, England, Cambridge University Press, 1937.

encloses remnants of the hyaloid artery. This mesoderm spreads out behind the lens and occupies the space taken by the corpus vitreum in the normal eye. The mesodermal band, as well as the mesodermal retrolenticular membrane (figs. 4 and 5) seen in these sections, is definitely overgrown, as compared with the retrolenticular tissue in

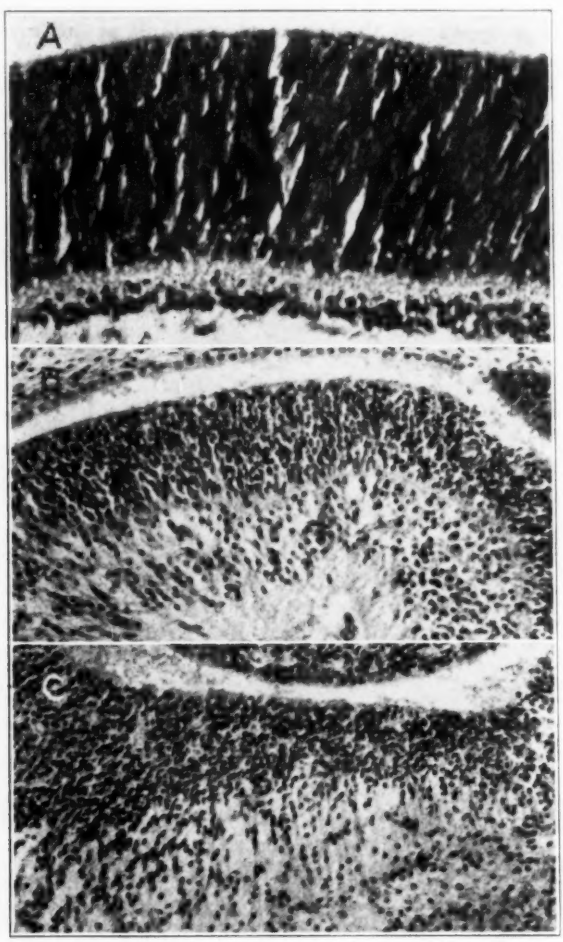

Fig. 7.—Sections of (*A*) retina of normal newborn rat; (*B*) retina of abnormal newborn rat enclosing space of the optic vesicle; (*C*) brain tissue of abnormal newborn rat, enclosing parts of lateral ventricle (approximately × 160).

normal fetuses. The changes in the lower parts of the optic cup—persistent fetal fissure, eversion of the retina and penetration of the cup by mesodermal tissue—are characteristic of the typical coloboma. In some abnormal eyes the posterior portions of the internal retinal leaf form many folds (figs. 5 and 6). These folds when cut transversely appear in the sections as "rosettes," in which the retinal cells are radially

arranged around a well definied inner circle. The space within this circle corresponds to the cavity of the fold, which is a part of the lumen of the optic vesicle. The histologic structure of the internal leaf of the retina shows little resemblance to that of the retina of a normal newborn rat. This is well borne out by a comparison of *A* and *B* of figure 7; in fact, the abnormal retina (fig. 7*B*) resembles brain tissue (fig. 7*C*) rather than normal retinal tissue. Hemorrhages are frequently seen in the abnormal eyes. They can be found in the orbits, in the cavity of the optic vesicle, in the retina and near the palpebral fissure.

In our opinion, the sections just discussed are representative of the congenital malformations of the eye found in the young of vitamin A–depleted rats. However, there were variations in the eyes of the 16 abnormal young that were examined histologically. As mentioned, the serial sections of all 32 eyes showed a fibrous retrolenticular membrane. In both eyes of 1 animal this membrane was apparently the only abnormality present. This rat was the only member of the litter that was carried to term. If there had been other fetuses in this litter, they were resorbed in the early stages of development. In 10 eyes the retrolenticular membrane was continuous with a thick strand of connective tissue which was embedded in the optic nerve and was carried along with it into the eye, but there were no signs of coloboma. In 13 eyes there were similar retrolenticular tissue and a retinal gap and eversion near the optic nerve, that is, coloboma of the disk. In 1 eye such a coloboma combined with a peripheral or anterior coloboma, but the two fissures were not continuous. Four eyes had complete colobomas, which were continuous from the region of the disk to the anterior part of the eye. In 30 eyes the structure of the retina was abnormal (fig. 7). In 28 eyes the iris and the ciliary body were rudimentary or abnormal, and in 28 eyes the anterior and posterior chambers were not formed. The mesoderm, which corresponds to the stroma of the cornea and of the iris, was partly or completely fused anteriorly with the conjunctival epithelium in 18 eyes and was fused posteriorly with the epithelium of the external retinal leaf in 30 eyes. The conjunctival sac was partly or completely occluded in 18 eyes. Seventeen of the 32 eyes sectioned were "open" and 15 closed. As a rule the character and degree of abnormalities were similar in litter mates. However, there were exceptions to this rule, and variations in the eyes of litter mates, as well as in the eyes of one and the same animal, were seen.

Most of the young with abnormalities of the eyes also had malformations of other soft tissues and of the skeleton. The changes observed in the other organs will be described in another communication. Although removed at term, the average weight of the young was only 3.4 Gm.

The following control experiments were undertaken. Eighty-six mothers of the Sprague-Dawley strain fed an adequate stock diet had

1,183 young which on careful inspection did not show "open eyes" at birth. Serial sections were made of the eyes of 20 of these young. None of the abnormalities just described were found in the 40 eyes examined. Sixty-four females of the same strain were raised on an adequate diet and bred on the purified diet W supplemented with 60 U. S. P. units of vitamin A daily. They had 423 young, none of which had open eyes at birth. Ten females were raised on the preparatory diet U and bred on the purified diet W supplemented with 60 U. S. P. units of vitamin A daily. They had 103 young, none of which were born with open eyes. The eyes of 18 of these young were

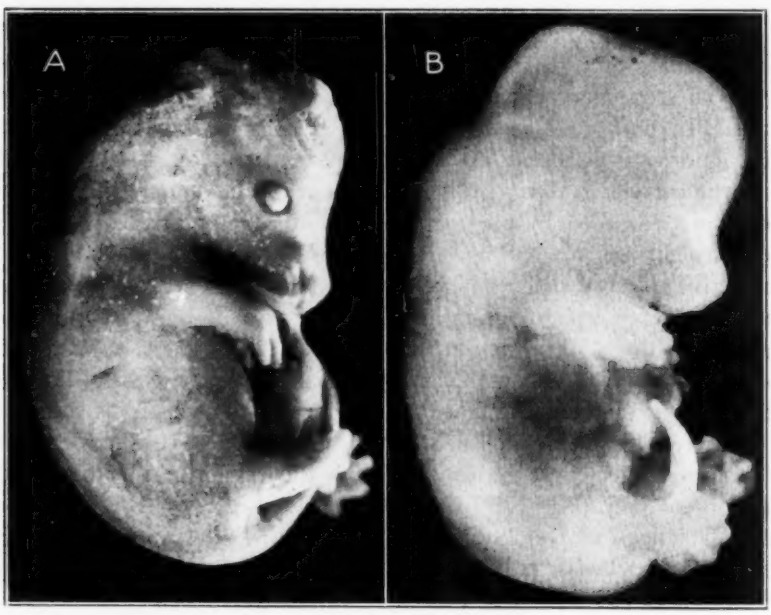

Fig. 8.—*A*, normal rat fetus approximately 16 days old; *B*, abnormal rat fetus approximately 16½ days old. The eye is not seen externally.

sectioned serially, and all 36 eyes were examined and found normal. Twelve females were raised on diet U and bred on diet W without giving birth to young. After they had lost about 40 Gm. of weight and had begun to show pronounced signs of vitamin A deficiency, they were given large amounts of vitamin A until they recovered and sexual cycles were restored. Then they were bred again and 54 young were obtained. None of these had open eyes. The eyes of 4 of these young were serially sectioned, and all 8 were found normal. Thus the abnormalities of the eyes described were found only in the young of mothers raised on diet U and bred on diet W. Female rats fed an adequate diet or diet W supplemented with vitamin A during pregnancy had young with normal eyes.[12]

(Footnote on next page)

EMBRYOLOGIC STUDIES

One hundred and fifty-four fetuses were removed between the fifteenth and the twentieth day of gestation from mothers reared on diet U and bred on diet W. The majority of these females were killed because they showed signs of beginning resorption. Many 15, 16 and 17 day old fetuses of this origin could be recognized externally as abnormal. The eyes of normal fetuses 15 to 17 days old have open palpebral fissures, since the lids do not develop and fuse before the eighteenth day of prenatal life. In most of the abnormal fetuses 15 to 17 days old the palpebral fissures could not be seen, and the eyes appeared absent or deeply embedded and removed from the surface (fig. 8 *B*).

Figure 9 illustrates the development of the normal eye from the fifteenth to the eighteenth day of prenatal life (*A*, *B*, *C* and *D*), as compared with the development of the abnormal eye (*E*, *F*, *G* and *H*). On the fifteenth day the normal eye (fig. 9 *A*) has an open palpebral fissure and is enclosed in a semicircular elevation which protrudes from between the rudimentary eyelids. The cornea lies on the surface of the body. It is a thin membrane, which consists of surface epithelium and one layer of mesodermal cells. The iris and ciliary body are not yet developed. The fetal fissure has closed. Between the lens and the retina a loose network of cells is seen, which consists of capillaries of the hyaloid system. The optic nerve is slightly closer to the lower than to the upper margin of the optic cup. Above the optic nerve the external leaf of the retina is somewhat thickened but well demarcated from the internal leaf. In the abnormal eye of a fetus of the same age (fig. 9 *E*) the lens is separated from the surface epithelium by mesodermal tissue which is much thicker than the normal cornea. The lens and the optic cup therefore appear far removed from the surface of the body. The cup is wide open near the optic nerve, since the retina is everted below the nerve. Through the opening enter, in addition to the optic nerve, the hyaloid artery and a band of mesodermal connective tissue which links extraocular mesoderm with the dense fibrous retrolenticular tissue. The everted parts of the retina decrease gradually in height. The coloboma illustrated in figure 9 *E* can be traced through anterior sections, which show that in this eye the fetal fissure is open its entire length.

In the section of the eye of a normal 16 day old embryo (fig. 9 *B*) it can be seen that the cornea has increased in thickness. The mesodermal tissue consists of several layers of cells and is posteriorly limited by an endothelium. A pupillary membrane divides the space

12. "Open eyes" were found in 3 of 2,000 young born of female rats of the Sprague-Dawley strain that had been bred on a diet deficient in riboflavin (Warkany, J., and Nelson, R. C.: Anat. Rec. **79**:83, 1941. Warkany, J., and Schraffenberger, E.: J. Nutrition **27**:477, 1944). These eyes were serially sectioned and showed no retrolenticular membrane and no coloboma. The iris and the retina were normal.

posterior to the cornea into two compartments. The optic nerve divides the cup into two equal parts. The lumen of the hyaloid artery can be seen in the center of the nerve stem. The layer of nerve fibers is developing in the internal leaf of the retina, and formation of the vitreous

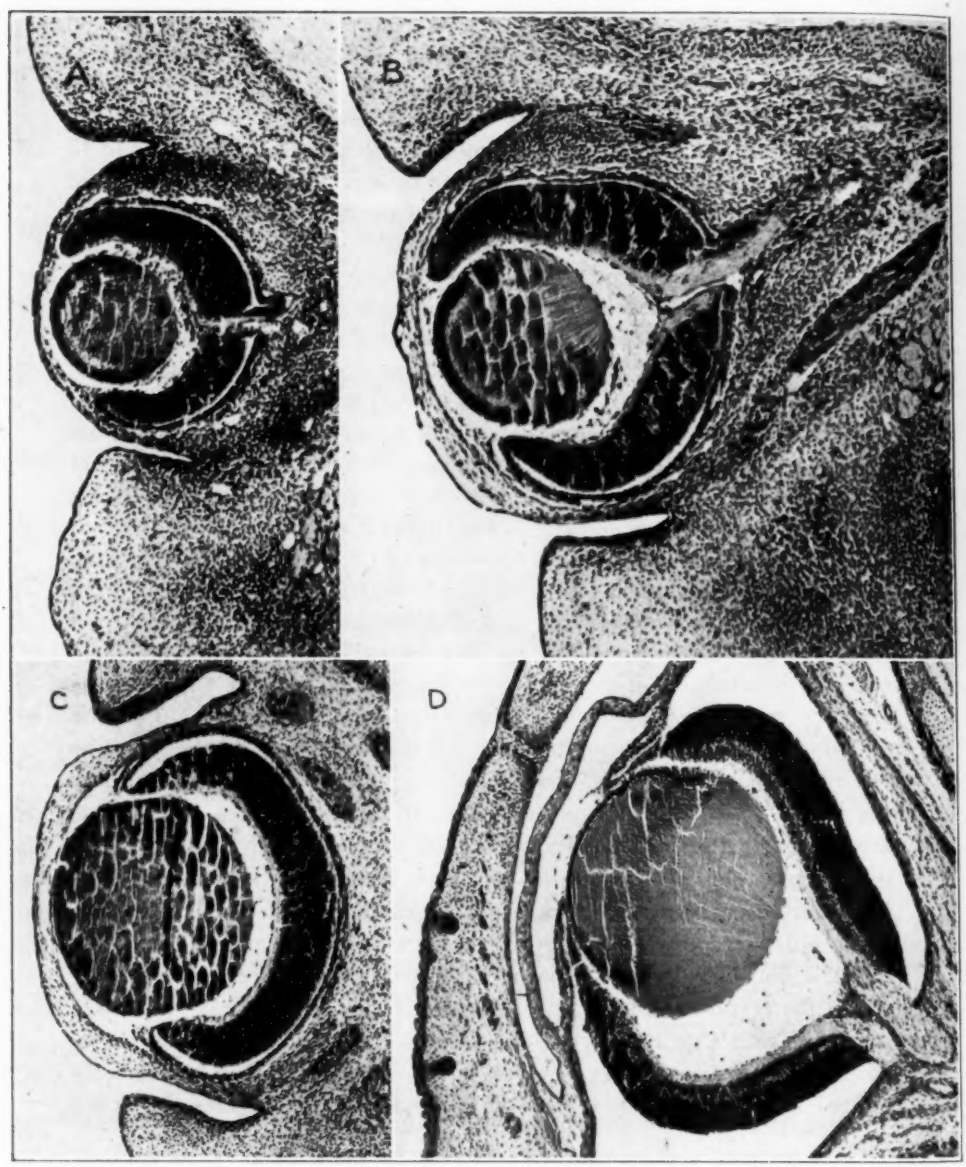

Fig. 9 *A-D.*—Sections of (*A*) eye of normal rat fetus approximately 15 days old; (*B*) eye of normal rat fetus approximately 16 days old; (*C*) eye of normal rat fetus approximately 17 days old; and (*D*) eye of normal rat fetus approximately 18 days old. (*A* and *B* approximately × 80; *C* and *D* approximately × 62.)

in the retrolenticular space has taken place. Few capillaries of the hyaloid system can be seen in this space. The abnormal eye (fig. 9 *F*) is separated from the surface by a thick layer of mesodermal tissue, which

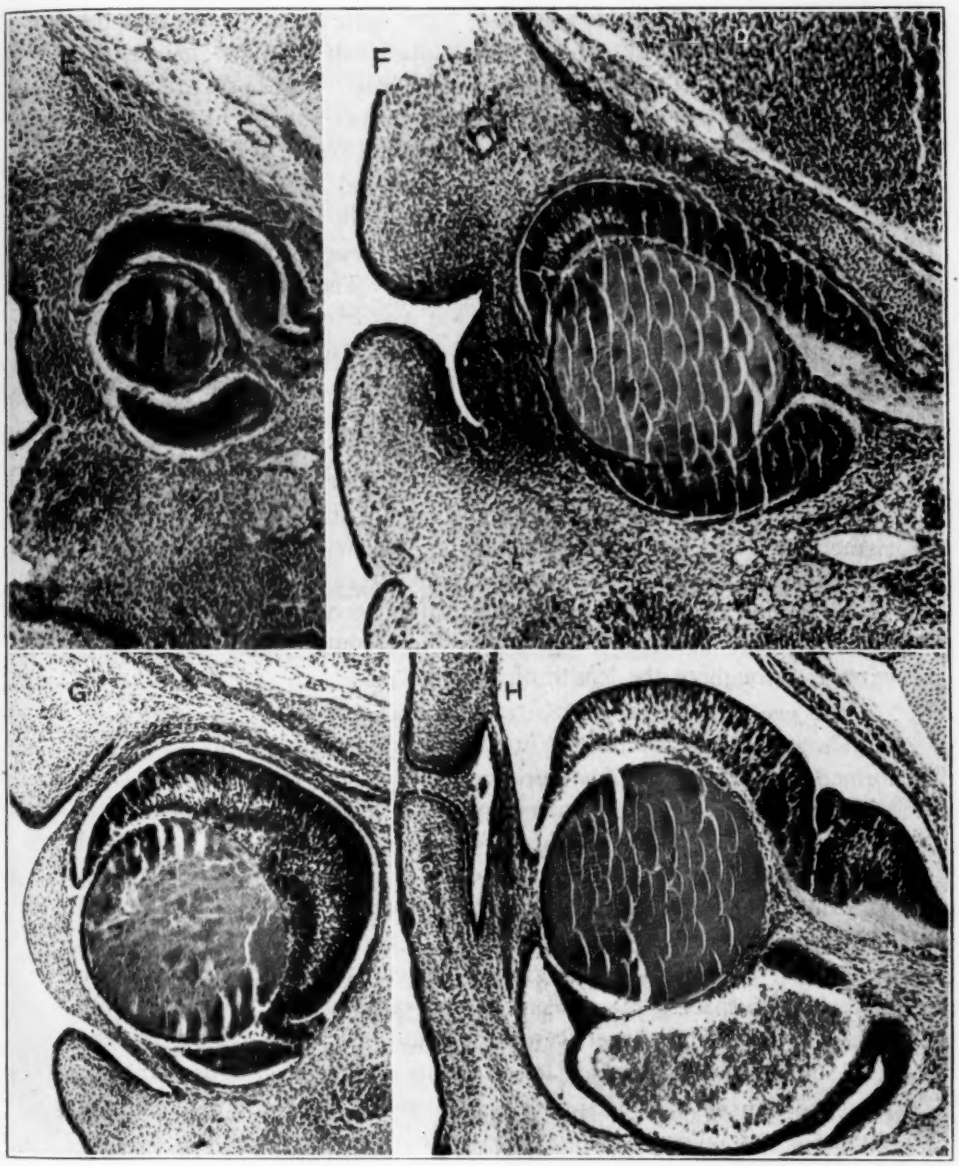

Fig. 9 *E-H.*—Sections of (*E*) eye of abnormal rat fetus approximately 15 days old; (*F*) eye of abnormal rat fetus approximately 16 days old; (*G*) eye of abnormal rat fetus approximately 17 days old; and (*H*) eye of abnormal rat fetus approximately 18 days old. (*E* and *F* approximately × 80; *G* and *H* approximately × 62).

is covered by surface epithelium. In front of the region of the eye two folds of skin are formed, which almost meet. The mesodermal tissue in front of the eye is in close contact with the anterior epithelium of the lens, so that the space usually present in the normal eye anterior to the lens appears entirely occluded. The optic nerve divides the optic cup into two unequal halves. The upper half is much longer and reaches farther forward than the lower half. Such proportions are seen in earlier embryonic stages of normal eyes but not in the normal 16 day old fetus. At this age they indicate an arrest of development.

Figure 9 *C* represents the eye of a normal 17 day old fetus; the section reproduced is ventral to the entrance of the optic nerve. The lids are still open. The chamber is well developed, but the iris is still absent. The vitreous is clearly seen. The internal leaf of the retina shows no formation of layers, but it is lined toward the vitreous by a stratum of nerve fibers. Figure 9 *G* illustrates the appearance of the eye of an abnormal 17 day old fetus. The anterior parts of this eye are normal; the lids are open; the cornea is of normal thickness, and a narrow chamber is seen. In contrast to the normal eye, there is a loose arrangement of the cells of the internal retinal leaf. The vitreous is absent, and its place is taken by a thin layer of connective tissue cells; this layer of retrolenticular fibrous tissue is much better developed in dorsal sections of the same eye. A cleft of the retina with eversion of the internal retinal leaf is seen in the lower part of the optic cup. This cleft represents a coloboma, which in this case extends throughout the length of the eye.

The eye of the normal 18 day old fetus (fig. 9 *D*) is covered by eyelids which are completely fused. A wide conjunctival space has formed; the cornea and the anterior chamber are well developed, and a primitive iris can be recognized. It consists of two layers, the distal one being a continuation of the external retinal leaf, which is covered toward the anterior chamber by cells of mesodermal origin. The posterior layer of the iris is the most anterior part of the internal retinal leaf. Between the two leaves the space of the optic vesicle can still be recognized. Between the margins of the cup the pupillary membrane is seen. The space of the vitreous has increased in size. In the internal leaf of the retina three layers can be distinguished: a dense outer nuclear layer, an inner nuclear layer of lesser density and the layer of nerve fibers. The blood vessel embedded in the optic nerve divides into numerous capillaries as soon as it reaches the vitreous.

The eye (fig. 9 *H*) of an abnormal 18 day old fetus is covered by lids which are completely fused. The conjunctival space exists in rudimentary form only. A thick layer of mesodermal tissue takes the place

of the cornea and of the anterior chamber. The margin of the optic cup represents the rudiments of the ectodermal parts of the iris. There is no vitreous, but a retrolenticular fibrous membrane is seen in its place. This membrane is linked with extraocular mesoderm by a band of connective tissue. There is a coloboma of the retina. The layers of the upper parts of the internal leaf of the retina are not well defined, and the structure of its lower parts has been destroyed by a hemorrhage. Blood cells can be seen below the lens and below the fibrous retrolenticular tissue.

The abnormal eyes of fetuses 19 to 21 days old resemble the eyes of mature abnormal young so much that it seems unnecessary to describe them here.

COMMENT

The experiments described in this report were planned as a study of the effects of extreme maternal vitamin A deficiency on the fetus. To this end the female rats of the parent generation were raised on a preparatory diet (diet U) which contained enough carotene to make possible growth and maturation but prohibited storage of vitamin A. At maturity the rats were placed on a purified diet (diet W) which was completely free of carotene and vitamin A. While on this diet the females were bred to normal males of the same strain. The mothers showed signs of vitamin A deficiency within one or two weeks, and their young presented, among other malformations, the ocular defects described. This method appears to induce a borderline deficiency in the mothers which in some instances permits termination of pregnancy at term, although the development of the young suffers. In other instances the females do not breed, or they resorb their young.

As controls, females of the same strain were raised and bred on an adequate diet. No congenital defects of the type described in this communication were found in the offspring. They were also absent in the offspring of females raised on the preparatory diet U and bred on diet W when the latter was supplemented with vitamin A. This permits the conclusion that vitamin A in the maternal diet prevents the defects in the young.

These congenital abnormalities of the eyes consist partly of structures arrested in early ontogenetic stages and partly of formations that do not correspond to normal embryonic conditions. The coloboma and eversion of the retina, its penetration by mesodermal tissue, the low insertion of the optic stalk in the cup, the absence of the chambers and the lack of fusion of the constituents of the iris can be explained by arrest of development. However, the overgrowth of connective tissue between the hyaloid vessels in the place of the vitreous and the peculiar structure of the retina have no equivalents in early fetal stages.

Some of the ocular malformations induced by maternal vitamin A deficiency resemble those seen in the defective eyes which are hereditary in certain strains of rabbits. These eyes, which have been thoroughly studied by von Hippel,[13] von Szily,[14] Koyanagi [15] and others, show coloboma, eversion of the retina and often microphthalmos and orbital cysts. However, the mesodermal tissue which enters the fetal fissure remains fine and delicate and is not always present. In the abnormal eyes described in this communication the corresponding mesodermal tissue is firm and closely knitted; it could be demonstrated in all abnormal eyes which were histologically examined. Orbital cysts and microphthalmos were not observed. These differences are of considerable theoretic interest, since the theories of causation of colobomas have been decidedly influenced by the changes observed in the eyes of rabbits of colobomatous stock.

The fact that a malformation such as coloboma, which has been observed as a hereditary defect, can also be induced by maternal dietary deficiency is in agreement with the conception [16] that a specific malformation can be the result of a genic mutation in 1 case and of an environmental modification in another. The coloboma induced by maternal nutritional deficiency represents a "phenocopy" [17] of the colobomas which are genetically determined.

In the description of the abnormal eyes we have emphasized certain anatomic features and have disregarded others which require further investigation. There is also need for additional experimental work which will aid in the explanation of the mechanism by which the defects are brought about. It is planned to ascertain the critical period in which the abnormalities are determined by supplementing the deficient diet with vitamin A on the various days of gestation, and experiments are in progress on the fate of some of the abnormal structures in postnatal life.

SUMMARY

When female rats were raised and bred on a dietary regimen which led to extreme vitamin A deficiency during pregnancy, congenitally deformed offspring were obtained. These newborn rats had various

13. von Hippel, E.: Arch. f. Ophth. **55**:507, 1903.

14. von Szily, A.: Ztschr. f. d. ges. Anat. (Abt. 1) **84**:1, 1924.

15. Koyanagi, Y.: Arch. f. Ophth. **104**:1, 1931.

16. Landauer, W.: Arch. f. Entwcklngsmechn. d. Organ. **110**:195, 1927. Dunn, L. C., in Harvey Lectures, 1939-1940, Lancaster, Pa., Science Press, 1940, pp. 135-165. Warkany, J.; Nelson, R. C., and Schraffenberger, E.: Congenital Malformation Induced in Rats by Maternal Nutritional Deficiency: IV. Cleft Palate, Am. J. Dis. Child. **65**:882 (June) 1943.

17. Goldschmidt, R. B.: Physiological Genetics, New York, McGraw-Hill Book Company, 1938.

defects of the skeleton and of some of the soft tissues. Histologic sections of the eyes were studied, and a fibrous retrolenticular membrane was found in place of the vitreous in every specimen. In addition, there were frequently colobomas, eversion and abnormal structure of the retina, rudimentary development of the iris and of the ocular chambers, defects of the cornea and of the conjunctival sac and lack of fusion of the lids. In case of the last defect the abnormal eyes could be recognized by external inspection. When the maternal diet was supplemented with vitamin A during pregnancy, the eyes of the young were normal.

CORNEAL TRANSPLANTATION AND PRELIMINARY IRIDECTOMY

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THE technic of corneal transplantation is a well established procedure. Iridectomy as a preliminary operation is here offered and recommended, for the following reasons:

(1) It enables the surgeon to estimate the amount of postoperative reaction that may follow in the eye concerned; (2) it allows for more rapid formation of the anterior chamber; (3) there is less likely to be a prolapse of the iris into the wound after the transplantation.

A preliminary iridectomy will enable the surgeon to study the eye involved under operative conditions. This does not apply so rigidly in cases in which an avascular nebulous cornea is present, such as may follow extensive phlyctenular keratitis or a central leukoma resulting from ulcer. But in cases of old interstitial keratitis resulting from syphilis or tuberculosis, in which infiltration is deep and the vascularity potentially marked, it is of value to determine the reaction that may result from a simple iridectomy before one does a major operation, such as a corneal transplantation. Severe keratitis has been observed to result from iridectomy in a case of the latter procedure. If the vascularity becomes marked, either a peritomy or cauterization of some of the larger vessels can be carried out to great advantage.

The reactivation of a previous underlying inflammatory process can result in an increase in intraocular tension, for in many cases of old interstitial keratitis there has been associated iritis or uveitis. In one of my cases low grade keratitis followed the iridectomy, and after this had subsided a rise in intraocular tension occurred (figure *A*). This was remedied by a filtering operation, before the eye was ready for corneal transplantation. It is better to deal with such complications before the final operation, as the graft will then have more favorable circumstances under which to adhere and remain transparent.

The development of glaucoma as a complication following corneal transplantation must be constantly kept in mind, and the surgeon should do everything in his power to avert this difficulty. The occur-

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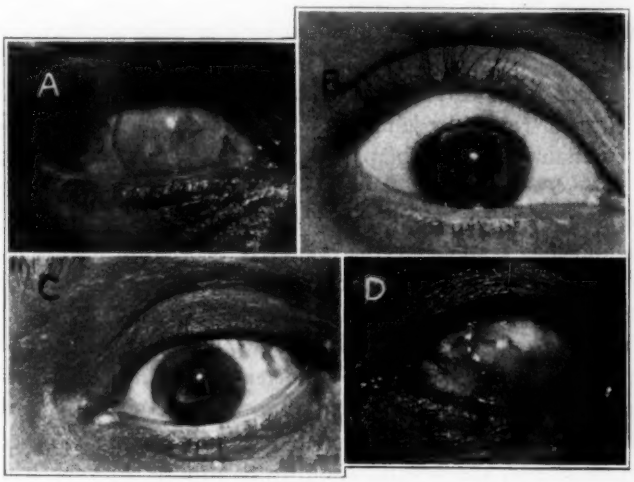
rence of this complication is frequently mentioned in case reports. Rapid reformation of the anterior chamber is essential to prevent adhesions at the chamber angle that may subsequently cause a rise in intraocular tension. If the graft and cornea of the recipient have been properly cut and the fit is as tight as it should be, the preliminary iridectomy will offer ideal conditions for a rapid reformation of the chamber. In all the 25 cases in which I carried out this procedure the anterior chamber was of normal depth within the first twenty-four hours. In 3 of these cases a second operation was performed because the graft had become opaque, and in none of them was there an increase in intraocular tension, all chambers reforming rapidly.



A, tuberculous interstitial keratitis; *B*, sclerectomy for glaucoma following a transplantation for keratoconus; *C*, hazy graft and prolapsed iris showing iridectomy; *D*, interstitial keratitis.

Two striking examples of the need of preliminary iridectomy to prevent glaucoma have been brought to my attention. After a transplantation for keratoconus, in the case illustrated in *B* there developed an increase in intraocular tension reaching 50 mm. of mercury (Schiøtz), with redness and edema of the cornea. A LaGrange sclerectomy was performed, and with miotics the tension was restored to normal and has remained so since, a period of one year. *C* of the figure illustrates a similar case. In this case an increase in intraocular tension developed after corneal transplantation. The iris became incarcerated on one edge of the wound, as can be seen in the illustration. The graft at no time was of normal transparency. After operation the intraocular tension gradually became elevated, and two months after the original operation an iridectomy was necessary. This controlled the

pressure. However, the graft must be done again if this patient is to benefit from a corneal transplant.

Experimentally, the clinical evidence for rapid reformation of the anterior chamber as related to iridectomy is not substantiated, for in the animals used (rabbits) the aqueous has an extremely rapid flow on opening the chamber and consequently the chamber is restored almost immediately.

A prolapse of the iris into the corneal wound is less likely to occur if preliminary iridectomy has been done. This is especially true if the anterior chamber has failed to resume its normal depth within a reasonable period. Also, if a cataract extraction is to follow the transplantation, the displacement forward of the vitreous which may follow removal of the lens may dangerously narrow the distance between the iris and the cornea, predisposing to postoperative glaucoma.

If relatively clear cornea is present near the periphery and the surgeon decides to place the graft away from the center of the cornea, near one limbal region, preliminary iridectomy in this spot will be especially valuable, as a prolapse of the iris would otherwise easily follow.

There is one group of cases in which an iridectomy may prove dangerous and may complicate the operative procedure that is to follow. It should be approached with caution in an eye which shows the relatively unfavorable deeply scarred, somewhat vascular cornea and in which when the anterior chamber is opened the iris is found to be smooth and bound down tightly to the lens or to its remnants. Loss of vitreous easily follows an iridectomy in such an eye, for the vitreous is often fluid as the result of the previous inflammatory process. If this condition exists, the wound should be sutured without iridectomy and the transplantation attempted later. *D* of the figure illustrates this type of eye.

The opinion has been voiced that preliminary iridectomy is unnecessary in such cases and merely subjects the eye to another surgical procedure. However, iridectomy is in itself a relatively simple operation and should not be feared if it will be a safeguard and help in performing a major operation later. *B* and *C* of the figure illustrate what can be avoided by carrying out this procedure.

SUMMARY

Iridectomy as a preliminary operation to corneal transplantation is recommended for the following reasons: (1) It enables the surgeon to evaluate how an eye will withstand surgical procedure; (2) the risk of glaucoma can be greatly lessened; (3) the possibility of prolapse of the iris is made unlikely.

10515 Carnegie Avenue.

CONTACT EYE CUP FOR CORNEAL BATHS WITH SOLUTIONS OF PENICILLIN

LIEUTENANT COLONEL GILBERT C. STRUBLE
AND
MAJOR JOHN G. BELLOWS
MEDICAL CORPS, ARMY OF THE UNITED STATES

THE value of local applications of solutions of penicillin in the treatment of certain inflammatory diseases of the eye is now generally recognized. Experimental and clinical evidence has shown this to be particularly true in cases of diseases of the anterior segment of the globe.[1] Experimentally, in cases of this type relatively high concentrations of penicillin in the cornea, conjunctiva, sclera, aqueous, iris and ciliary body and small amounts in the vitreous can be built up by use of the corneal bath and by subconjunctival injection.[2] High degrees of penetration of penicillin have also been attained with iontophoresis.[3]

It has been our experience that administration of penicillin as eye drops by simple instillation will effect the prompt cure of the acute inflammatory diseases of the conjunctiva caused by penicillin-sensitive organisms.[2] In the treatment of corneal ulcers, however, particularly in cases in which the deeper layers of the cornea are involved, the instillation of penicillin locally as eye drops, even though done every hour, has proved inadequate. This is due to the rapid loss of the penicillin through the lacrimal apparatus, to rapid dilution with the tears and to diffusion.

The corneal bath is a simple method of producing a high content of the drug in the tissues of the anterior segment of the globe.[2] Such concentrations are desirable in cases of deep corneal infection, such as serpent ulcer. The ordinary commercial eye cup is found to be unsatisfactory, for the following reasons:

From the Department of Ophthalmology, Billings General Hospital, Fort Benjamin Harrison, Ind.

1. Robson, J. M., and Scott, G. I.: Local Chemotherapy in Experimental Lesions of the Eye, Lancet **1**:100, 1943. von Sallmann, L.: Penicillin and Sulfadiazine in the Treatment of Experimental Intraocular Infection with Pneumococcus, Arch. Ophth. **30**:426 (Oct.) 1943; Penicillin and Sulfadiazine in the Treatment of Experimental Intraocular Infections with Staphylococcus Aureus and Clostridium Welchii, ibid. **31**:54 (Jan.) 1944.

2. Struble, G. C., and Bellows, J. G.: Studies on the Distribution of Penicillin in the Eye and Its Clinical Application, J. A. M. A. **125**:685 (July 8) 1944.

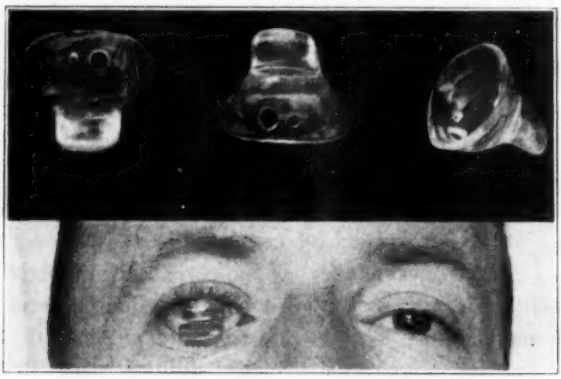
3. von Sallmann, L., and Meyer, K.: Penetration of Penicillin into the Eye, Arch. Ophth. **31**:1 (Jan.) 1944.

1. An excess of penicillin solution is required to fill the cup, and a considerable amount is lost through leakage and through the lacrimal apparatus.

2. The corneal lesions become contaminated from the surfaces of the skin and lashes.

The patient experiences difficulty in keeping the eye open because of the pain and blepharospasm associated with the corneal ulcer.

With the technical aid of Major George Powell, a suitable eye cup has been designed for corneal baths; obviously, it should prove satisfactory in the treatment of various conditions requiring corneal baths, for example, the application of miotics in cases of acute glaucoma. The contact cup is made of a clear acrylic material. It has a small knob or handle attached to its anterior curved surface to facilitate handling. Located in the upper margin are two small round openings, the larger



Above, anterior, lateral and posterior views of the contact cup; below, contact cup in place.

for the instillation of the penicillin solution and the smaller for the escape of air during the process of filling the cup. This cup rests on the scleral conjunctiva under the lids, effecting an air-tight and water-tight seal. It has proved entirely satisfactory in our hands.

Cold sterilization in a solution of mercury bichloride is easily carried out. The cups should not be boiled, autoclaved or sterilized in any solution containing chloroform or ether, which are solvents of the acrylic material.

The eye to be treated is first anesthetized by the instillation of a few drops of any of the anesthetics for local use in the eye, such as tetracaine, butacaine, metycaine or phenacaine. With the patient looking down, the upper margin of the contact cup is then slipped under the upper lid; the patient is then directed to look up, so that the lower margin of the cup will drop into the lower cul-de-sac, inside the lower lid.

The cup is then filled with the prepared solution of penicillin by injecting the solution into the larger round hole, at the top of the cup. For this purpose, we have found a tuberculin syringe most suitable, using an ordinary hypodermic needle, the tip of which has been cut off and blunted. Filling is facilitated by directing the patient to look down and slightly elevating the upper lid with a finger of the left hand while injecting the fluid from the syringe with the right. During this procedure the patient may be either lying on his back or sitting erect. We prefer the latter position.

The strength of the penicillin solution used by us has varied from 1,000 to 2,500 Oxford units in 1 cc. of isotonic solution of sodium chloride. We have found these dilutions to be entirely free from undesirable side effects, such as burning or smarting. The duration of the first treatment is thirty minutes, with subsequent treatments extending up to one hour. This procedure should be repeated at intervals of four to five hours in order to maintain an adequate level of penicillin in the cornea and aqueous.

The advantages of the contact bath cup are as follows:

1. Known concentrations of penicillin can be kept in contact with the anterior segment of the globe for long periods. There is no loss of fluid through the lacrimal apparatus, nor is there dilution of the solution by the tears.

2. Considerable conservation of penicillin is possible. Less than 0.5 cc. of solution is required to fill the cup.

3. With adequate anesthesia the patient experiences no discomfort whatever.

4. The transparent cup permits a view of the anterior segment of the globe and the level of the penicillin solution at all times.

5. The contact cup fits either eye.

Major George Powell, director of the Dental Section of the Medical Department Enlisted Technicians School, Billings General Hospital, Fort Benjamin Harrison, Ind., gave technical assistance.

Clinical Notes

TRAUMATIC LIPORRHAGIA RETINALIS

Report of a Case

CAPTAIN OGDEN D. PINKERTON
Medical Corps, Army of the United States

TRAUMATIC liporrhagia retinals, commonly known as Purtscher's disease, or the syndrome of the posterior pole of the eyeball, is characterized by exudation and hemorrhage in the posterior pole of a nontraumatized eye, followed (in some cases) by atrophy of the optic nerve. Precipitating factors are head injury, fractures of the vertebrae and long bones and compression injuries of the chest. In the case presented the lesion was unilateral, related to both the arterioles and the venules and terminated in almost complete atrophy of the optic nerve.

The photographs of the fundus show the advanced degree of atrophy of the optic nerve and the organized exudate in the macular area (fig. *A* and *B*).

REPORT OF CASE

History.—A Filipino boy aged 11 was struck and knocked to the ground by an Army vehicle on June 9, 1944. He was not rendered unconscious, but he stated that his breath was "knocked out." He was admitted to the hospital in shock, with a blood pressure of 94 systolic and 42 diastolic. Examination revealed: (1) a severe lacerated wound of the left temporal and frontal areas and the left external canthus; (2) compound, comminuted, complete fracture of the anterior end of the left zygomatic bone, and (3) contusions of both sides of the face, the lower left anterior wall of the chest and the upper portion of the abdomen on both sides. The patient was mentally clear, and there was no evidence of cerebral concussion or damage.

About twenty-eight hours after admission the patient reported that he was unable to see with his right eye.

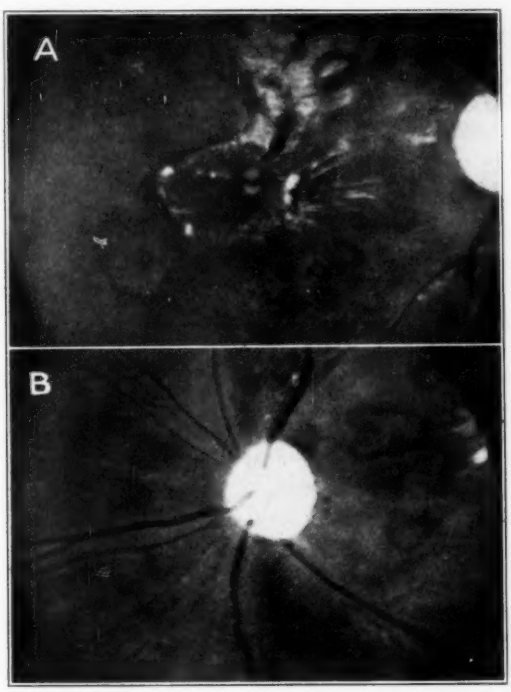
Ocular Examination.—Examination six hours later revealed the following condition: Right Eye: Visual acuity was limited to perception of light peripherally, with very poor projection. There was no external evidence of injury of the eyeball, lids, conjunctiva or orbital rim. The pupil was semidilated and reacted sluggishly to light and in binocular accommodation.

Left Eye: Visual acuity was 20/20. The eyelids were ecchymotic. There were a large temporal conjunctival hemorrhage and a repaired laceration of the external canthus. The pupillary reactions were normal.

Fundi: Examination of the fundus of the nontraumatized, right, eye revealed a dense, yellowish white reflex, confined to the posterior pole. This was due to a massive yellow extravasation, which extended about 3 disk diameters superiorly, 4 disk diameters nasally, 5 disk diameters inferiorly and 4' disk diameters temporally. The arteries and veins were distinctly made out and were not covered by exudate. The exudate showed no specific relation to the arterioles or venules, being evenly dispersed between the vessels. The vessels appeared as distinct

channels on a yellowish white background. The veins were engorged. The nerve head was surrounded by exudate, but its margins were flat. There were many fresh, striated hemorrhages above and below the disk and between the disk and the macula. The hemorrhages were located along both the venules and the arterioles. The macula presented a well circumscribed, deep hemorrhage. The fundus of the traumatized eye revealed no pathologic change.

Six days later considerable peripheral absorption of the exudate had taken place. The macula presented a triangle of various colors. Centrally, it was of chocolate hue, surrounded by a ring of grayish brown, and this, in turn, was surrounded by a halo of yellow. Thirteen days after the boy's admission there was no noticeable change in the hemorrhages, but the exudate had continued to



Photographs taken three months after injury, showing organized exudate in (*A*) the macular area and (*B*) atrophy of the optic nerve head.

diminish. Thirty-one days after his admission there was complete absorption of the exudate and hemorrhage except for a small amount between the nerve head and the macula. The nerve head now presented a pronounced generalized pallor. Vision was limited to counting fingers at 3 to 4 feet (90 to 120 cm.) in the temporal and superior fields only, with marked restriction of these fields.

The cholesterol content of the blood, determined three days after the patient's admission, was normal. Roentgenographic studies revealed no fractures of the orbit or the optic foramen.

Three weeks after the patient's admission to the hospital there developed atypical pneumonia of the upper lobe of the right lung and, later, of the upper lobe of the left lung; both areas cleared prior to his discharge from the hos-

pital. Three months after his discharge there was a recurrence of consolidation in the upper lobe of the left lung, accompanied with cough and fever. The patient is still hospitalized, one year later, with a diagnosis of abscess of the lung. It is doubtful that the injury precipitated the pathologic condition in the chest.

Photographs of the fundus of the right eye taken three months after injury revealed atrophy of the optic nerve and scarring in the macular area.

Abstracts from Current Literature

EDITED BY DR. WILLIAM ZENTMAYER

Bacteriology and Serology

BACTERIOLOGIC STUDY OF HUMAN CONJUNCTIVAL FLORA. F. H. RODIN, Am. J. Ophth. **28:** 306 (March) 1945.

Rodin emphasizes the value of bacteriologic study of conjunctival infections. He gives his observations in 152 cases of clinically normal conjunctivas from birth to 80 years of age. It is considered advisable to postpone operation for cataract in the presence of six or more colonies of hemolytic staphylococci or of 2 or more of hemolytic streptococci, Pneumococcus or Bacillus pyocyaneus.

W. S. REESE.

Conjunctiva

SOME OBSERVATIONS ON THE CHEMICAL NATURE OF THE PTERYGIUM. H. H. BEARD and T. J. DIMITRY, Am. J. Ophth. **28:** 303 (March) 1945.

Three pterygiums were studied after surgical removal. Their average weight was about 8 mg. The chloroform-soluble material amounted to about 47.5 per cent of the fresh weight of the growth. A positive Salkowski reaction for cholesterol was obtained, but the amount present was too small to be precipitated with digitonin. The action of choline chloride in producing alterations in these growths is discussed, together with a new etiologic theory of the disease.

W. S. REESE.

General Diseases

BILATERAL TEMPORAL ARTERITIS WITH COMPLETE LOSS OF VISION. E. W. SHANNON and J. SOLOMON, J. A. M. A. **127:** 647 (March 17) 1945.

A white man aged 73 complained of severe headache and loss of vision, with severe pains in the jaws. Vision in each eye was limited to questionable perception of light. The crystalline lens showed opacities. In each eye there was edema of the retina and papilla with venous engorgement and some minute hemorrhages. A segment of the right temporal artery was removed. The vessel was grossly thrombosed. Three weeks after the operation the headache was almost entirely gone. The eyes were now blind.

In a case of bilateral temporal arteritis with complete loss of vision in both eyes, a section of one of the temporal arteries revealed the characteristic picture as described by Horton. The cause of the visual loss is not known, primarily because there has been no autopsy in any of the cases of temporal arteritis. It has been suggested that the retinal artery is the site of a pathologic process similar to that described in the

temporal artery. One investigator has actually worked out an anastomosis between the temporal artery and the retinal vein. Other theories have been advanced.

W. ZENTMAYER.

Glaucoma

CONGENITAL GLAUCOMA AND CATARACT, BILATERAL, GONIOTOMY AND NEEDLING. T. D. ALLEN, Am. J. Ophth. **28:** 388 (April) 1945.

Allen cites the case of a 5 month old child with bilateral glaucoma and an associated cataract in which he did goniotomies by inserting the goniotomy knife at the limbus of the cornea and passing it across the pupil and sweeping down into the angle in the inferior nasal quadrant. Four operations were performed on the left eye. No contact glass was used. A single similar procedure was used on the right eye.

The tension when the patient was under narcosis was 31 and 46 mm. in the two eyes; this was reduced to 20 and 16 mm. of mercury. A single needling of the lens was done in each eye.

This method is not advocated as universally applicable in all cases of deep chamber glaucoma or in all cases of hydrophthalmos; it is merely intended to record what has been accomplished in this 1 case.

W. ZENTMAYER.

Injuries

PERFORATING OCULAR INJURIES. A. C. SNELL JR., Am. J. Ophth. **28:** 263 (March) 1945.

In an analysis of 172 cases of perforating ocular injuries, the following factors are seen to have a reasonably consistent unfavorable influence on the chances for recovery: (1) injuries with blunt objects, (2) double perforation of the globe, (3) major degrees of prolapse of the intraocular contents, (4) large intraocular hemorrhage and (5) intraocular infection. On the other hand, recovery is not consistently influenced by (1) the length of the laceration, (2) the location of the laceration, (3) injury to the lens, (4) prolapse of the iris or (5) minor degrees of hemorrhage. The interrelation of some of these complications is discussed. The (corrected) incidence of sympathetic ophthalmia among these cases is 1.45 per cent.

In the choice of methods of repair of corneal lacerations, the use of a conjunctival flap and the employment of direct corneal sutures appear to be about equally efficacious. Other features in the management of perforating ocular injuries are discussed.

W. S. REESE.

Lacrimal Apparatus

DACRYOCYSTITIS: THE PART PLAYED BY SYPHILIS IN ITS ETIOLOGY. J. O. WETZEL, Am. J. Ophth. **28:** 511 (May) 1945.

In comparatively few cases of dacryocystitis has syphilis been recognized as the etiologic factor. It is probable that more careful laboratory examinations might reveal many unsuspected cases. Therefore it would seem desirable that serologic tests become a regular part of the examination in all cases in which the causal factor is in doubt.

W. S. REESE.

Lids

DERMATITIS OF THE LIDS FROM PENICILLIN EYE DROPS. ELIAS SELINGER, J. A. M. A. **128:** 437 (June 9) 1945.

Various untoward reactions to penicillin have been reported in the literature. Urticaria has been observed to result from the systemic administration of the drug, and cutaneous rashes from direct contact with the substance and the solution of penicillin. In some instances the reaction was thought to be the result of contaminants rather than of the drug itself.

A man aged 53 had been treated for bilateral conjunctivitis for about one year. A solution of penicillin sodium containing 250 Oxford units of penicillin per cubic centimeter in isotonic solution of sodium chloride was prescribed, with instructions to instill 1 drop in each eye every two hours. The patient used this solution for four days, when he returned to the office because there was no improvement in the conjunctivitis. He thought a more concentrated solution might be more effective. Although at that time the skin of the upper lids seemed slightly edematous and somewhat shiny, its appearance was not accepted as an early sign of contact dermatitis, as it would have been if other medication had been used. A solution containing 500 Oxford units per cubic centimeter was prescribed. The following day the patient returned to the office with a typical picture of contact dermatitis. The skin of the lower lids was thickened, red and shiny. The redness of the lids was particularly pronounced along the side of the nose, where the excess of the solution had trickled down over the cheeks. The skin of the upper lids, especially near the inner canthi, was edematous but not red. The conjunctivas showed no reaction, and the corneas, examined with a slit lamp, were also free from reaction. A patch test gave negative results. No history of urticaria, hay fever or other allergic manifestations could be elicited. The dermatitis cleared up five days after penicillin was discontinued.

The noteworthy features of this case are the absence of any conjunctival irritation in spite of the rather pronounced dermatitis of the lids and the occurrence of the dermatitis in a person apparently not subject to allergic disturbances.

Incidentally, the results of penicillin therapy in 3 cases of acute and in 9 cases of chronic catarrhal conjunctivitis were no better than those with the older therapeutic agents.

W. ZENTMAYER.

Methods of Examination

THE SPACE EIKONOMETER TEST FOR ANISEIKONIA. A. AMES JR., Am. J. Ophth. **28:** 248 (March) 1945.

Ames describes the space eikonometer and the method of using it. Its use requires less time and provides an easier discriminative task for the patient than does the standard eikonometer procedure.

W. S. REESE.

Ocular Muscles

SOME OBSERVATIONS ON DIVERGENT STRABISMUS WITH ANOMALOUS RETINAL CORRESPONDENCE. H. W. GRANT, Am. J. Ophth. **28:** 472 (May) 1945.

Twenty-two cases of divergent strabismus with constant anomalous correspondence were studied from the standpoint of diagnosis and treatment. The fusion was so poor in some instances as to make the afterimage test unreliable.

On the basis of the therapeutic results the cases are divided into three main groups: 1. Cases with poor convergence which were incurable, the deviation tending to assume its original amount and characteristics after surgical correction. Convergence exercises helped to reduce the cosmetic defect, but the improvement was not maintained.

2. Cases with good convergence in which the deviation could be corrected surgically. Severe asthenopic symptoms and incongruous diplopia were present for years after surgical correction.

3. Cases of horror fusionis with total or partial anomalous correspondence which was completely relieved by extreme care in correcting the refractive error.

W. S. REESE.

Pharmacology

THE EFFECT OF DETERGENT ON THE PENETRATION OF SODIUM SULPHACETAMIDE (ALBUCID SOLUBLE) INTO OCULAR TISSUES. M. GINSBURG and J. M. ROBSON, Brit. J. Ophth. **29:** 185 (April) 1945.

The penetration of sodium sulfacetamide into the ocular tissues was studied both in living rabbits and in isolated ocular tissues. The application of the drug with a wetting agent, Duponol ME dry, increases the penetration of sodium sulfacetamide into and through the cornea. Removal of the corneal epithelium results in a great increase in the penetration of the sulfonamide drug into and through the cornea; that is, the epithelium acts as a barrier to the passage of the drug. The wetting agent does not increase the passage of the drug into the denuded cornea (i. e., the cornea with the epithelium removed). It may be concluded that the wetting agent acts by overcoming the epithelial barrier. The results suggest that addition of a wetting agent to sodium sulfacetamide is of most value with infections of the cornea and iris.

W. ZENTMAYER.

Retina and Optic Nerve

IODIDE THERAPY FOR SENILE MACULAR DEGENERATION. R. G. LAIRD, Am. J. Ophth. **28:** 287 (March) 1945.

The factors which produce senile macular degeneration are thought to be (*a*) senility, (*b*) heredity and (*c*) sclerosis of the choriocapillaris of the choroid. It is probable that heredity is the major factor in many instances, for it may predispose to either senility or sclerosis of the choriocapillaris.

The administration of iodides appreciably improved the vision in a majority of cases of senile macular degeneration in this series. The

mechanism by which this improvement is obtained is not known. Large doses of iodides are not necessary to obtain satisfactory results.

W. S. REESE.

OBSERVATIONS ON RETINAL BLOOD FLOW WITH THE AID OF KUKAN'S OPHTHALMODYNAMOMETER. M. W. MORGAN JR., J. B. MOHNEY and J. M. OLMSTED, Am. J. Ophth. **28:** 749 (July) 1945.

Application of Kukan's cup to the eye of the cat under pentobarbital anesthesia increases the intraocular pressure sufficiently to stop the blood flow in the retinal vessels.

Stimulation of the cervical sympathetic fibers increases the blood flow in the retinal vessels, probably because of the increased blood pressure outside the eyeball.

Sensory fibers in the long ciliary nerves can reflexly increase the blood flow in retinal vessels, evidently by this same mechanism, since the effect is produced when both the long and the short ciliary nerves are cut.

W. S. REESE.

ABERRANT OPTIC NERVE FIBERS FOUND BETWEEN RETINA AND HEXAGONAL CELLS. A. LOEWENSTEIN, Brit. J. Ophth. **29:** 180 (April) 1945.

Two cases of aberrant nerve fibers of the optic nerve of different sizes are described. The first type was found in a case of pigmented tumor of the optic disk infiltrating the neighboring retina and choroid. The lesion is assumed to be a malignant degeneration of a pigmented nevus of the optic disk. This type involves maldevelopment of the posterior retinal layers in front of the growth. The second type was seen in a case of hypertensive retinopathy with edematous swelling of the papilla and a large druse. The nerve fiber tissue found between the retina and the pigmented epithelium was degenerated in a ganglioform manner. The retina in front of this tissue was well developed. A mechanical pushing out of the optic nerve fibers, due to the edema and the pressure of the druse, is assumed to be the cause.

The article is illustrated.

W. ZENTMAYER.

Tumors

ERRORS IN DIAGNOSIS OF INTRAOCULAR TUMORS. W. E. BRUNER, Am. J. Ophth. **28:** 297 (March) 1945.

Bruner reports 7 cases of intraocular tumor and discusses them from the standpoint of diagnosis, management and final outcome.

W. S. REESE.

News and Notes

UNIVERSITY NEWS

Ophthalmologic Seminar, Emory University School of Medicine.—Emory University School of Medicine will celebrate the one-hundredth anniversary of the birth of Abner Wellborn Calhoun, L.D., LL.D., who was born April 16, 1845 and died Aug. 21, 1910, the first professor of ophthalmology of the Atlanta Medical College.

You are cordially invited to be the guest of Emory University at an ophthalmologic seminar, to be held in Atlanta, Ga., April 4, 5 and 6, 1946.

The following papers will be presented:

April 4: Evening: "Myasthenia Gravis," Dr. Frank B. Walsh; "Medical Ophthalmology," Dr. Walter I. Lillie.

April 5: Morning: "Diplopia," Dr. Walter I. Lillie; "Clinical Meaning of Exophthalmos," Dr. William Benedict.

Afternoon: "Ocular Changes in Diabetes," Dr. Derrick Vail; "Nasopharyngeal Tumors," Dr. Frank B. Walsh.

Evening: "Ocular Therapeutics in Glaucoma," Dr. Parker Heath; "Treatment of Detachment of the Retina," Dr. John Dunnington.

April 6: Morning: "Glaucoma in Diabetes," Dr. William Benedict; "Surgical Treatment of the Vertical Deviations," Dr. John Dunnington.

Afternoon: "Random Notes on Ocular Surgery," Dr. Parker Heath; "Ocular Signs of Subdural Hematoma," Dr. Frank B. Walsh; "Clinical Diagnosis of Retrobulbar Neuritis," Dr. Walter I. Lillie.

Evening: "Preparation of the Patient for Cataract Operation," Dr. William Benedict; "Circulation of the Optic Nerve and Its Influence on Disease," Dr. Derrick Vail.

For further information, address Dr. Eugene Stead, Dean, 50 Armstrong Street, S.E., Atlanta, Ga.

GENERAL NEWS

American Orthoptic Council: Examinations for Technicians.—The next examination by the American Orthoptic Council will he held in September and October 1946.

The written examinations will be held at various cities in the country on Friday, September 6. Only those passing the written examinations will be permitted to take the oral and practical tests, to be given in Chicago, Saturday, October 12.

Applications on official forms must be received before July 1, 1946.

Address the American Orthoptic Council, 23 East Seventy-ninth Street, New York 21.

Oregon Academy of Ophthalmology and Otolaryngology.—The sixth annual spring postgraduate course in ophthalmology and otolaryngology will be held in Portland, Ore., April 15 to 20, 1946. Dr. Algernon B. Reese, professor of ophthalmology, Columbia University, New York, and Dr. Gabriel Tucker, professor of bronchoscopy and laryngology, University of Pennsylvania Graduate School, Philadelphia, will be guest speakers.

Directory of Ophthalmologic Societies*

INTERNATIONAL

International Association for Prevention of Blindness

President: Dr. P. Bailliart, 66 Boulevard Saint-Michel, Paris, 6e, France.
Secretary-General: Prof. M. Van Duyse, Université de Gand, Gand, Prov. Ostflandern, Belgium.
All correspondence should be addressed to the Secretariat, 66 Boulevard Saint-Michel, Paris, 6e, France.

International Ophthalmologic Congress

President: Prof. Nordenson, Serafimerlasarettet, Stockholm, Sweden.
Secretary: Dr. Ehlers, Jerbanenegade 41, Copenhagen, Denmark.

International Organization Against Trachoma

President: Dr. A. F. MacCallan, 17 Horseferry Rd., London, England.

Pan-American Congress of Ophthalmology

President: Dr. Harry S. Gradle, 58 E. Washington St., Chicago.
Executive Secretaries: Dr. Conrad Berens, 35 E. 70th St., New York. Dr. M. E. Alvaro, 1511 Rua Consolacão, São Paulo, Brazil.

FOREIGN

All-India Ophthalmological Society

President: Dr. B. K. Narayan Rao, Minto Ophthalmic Hospital, Bangalore.
Secretary: Dr. G. Zachariah, Flitcham, Marshall's Rd., Madras.

British Medical Association, Section on Ophthalmology

President: Dr. W. Clark Souter, 9 Albyn Pl., Aberdeen, Scotland.
Secretary: Dr. Frederick Ridley, 12 Wimpole St., London, W. 1.

Chengtu Ophthalmological Society

President: Dr. Eugene Chan.
Secretary: Dr. K. S. Sun.
Place: Eye, Ear, Nose and Throat Hospital, Chengtu, China.

Chinese Ophthalmology Society

President: Dr. C. H. Chou, 363 Avenue Haig, Shanghai.
Secretary: Dr. F. S. Tsang, 221 Foochow Rd., Shanghai.

Chinese Ophthalmological Society of Peiping

President: Dr. H. T. Pi, Peiping Union Medical College, Peiping.
Secretary: Dr. C. K. Lin, 180 Hsi-Lo-yen Chienmeng, Peiping.
Place: Peiping Union Medical College, Peiping. Time: Last Friday of each month.

* Secretaries of societies are requested to furnish the information necessary to make this list complete and keep it up to date.

Faculty of Ophthalmologists

President: Brig. Sir Stewart Duke-Elder, 63 Harley St., London, W. 1, England.
Secretary: Mr. Frank W. Law, 45 Lincoln's Inn Fields, London, W. C. 2, England.

German Ophthalmological Society

President: Prof. W. Lohlein, Berlin.
Secretary: Prof. E. Engelking, Heidelberg.

Hungarian Ophthalmological Society

President: Prof. I. Imre, Budapest.
Assistant Secretary: Dr. Stephen de Grósz, University Eye Hospital, Máriautca 39, Budapest.
All correspondence should be addressed to the Assistant Secretary.

Midland Ophthalmological Society

President: Dr. W. Niccol, 4 College Green, Gloucester, England.
Secretary: Mr. T. Harrison Butler, 61 Newhall St., Birmingham 3, England.
Place: Birmingham and Midland Eye Hospital.

North of England Ophthalmological Society

President: Mr. E. F. Wilson, 24 Upper Northgate St., Chester.
Secretary Mr. William M. Muirhead, 70 Upper Hanover St., Sheffield 3.
Place: Manchester, Leeds, Newcastle-upon-Tyne, Liverpool, Sheffield and Bradford, in rotation. Time: October to May.

Ophthalmological Society of Australia

President: Dr. J. Ringland Anderson, Astor House, 108 Collins St., Melbourne, Victoria.
Secretary: Dr. D. A. Williams, 27 Commonwealth St., Sydney.
Place: Melbourne. Time: Oct. 20-26, 1946.

Ophthalmological Society of Egypt

President: Prof. Dr. Mohammed Mahfouz Bey, Government Hospital, Alexandria.
Secretary: Dr. Mohammed Khalil, 4 Baehler St., Cairo.
All correspondence should be addressed to the secretary, Dr. Mohammed Khalil.

Ophthalmological Society of Hospital de Nuestra Señora de la Luz

Chairman: Dr. Manuel J. Icaza y Dublán, México, D. F., Mexico.
Secretary: Dr. Jorge Meyrán, México, D. F., Mexico.

Ophthalmological Society of South Africa

President: Dr. A. W. Sichel, National Mutual Bldg., Church Square, Cape Town.
Secretary: Dr. J. K. de Kock, Groote Kerk Bldg., 32 Parliament St., Cape Town.

Ophthalmological Society of the United Kingdom

President: Mr. Charles B. Goulden, 89 Harley St., London.
Secretary: Mr. Frank W. Law, 30 Devonshire Pl., London, W. 1.

Ophthalmology Society of Bombay

President: Dr. D. D. Sathaye, 127 Girgaum Rd., Bombay 4, India.
Secretary: Dr. H. D. Dastur, Dadar, Bombay 14, India.
Place: H. B. A. Free Ophthalmic Hospital, Parel, Bombay 12. Time: First Friday of every month.

Oxford Ophthalmological Congress

Master: Mr. P. G. Doyne, 60 Queen Anne St., London, W. 1, England.
Secretary-Treasurer: Dr. F. A. Anderson, 12 St. John's Hill, Shrewsbury, England.
Time: July 4-6, 1946.

Palestine Ophthalmological Society

President: Dr. Arieh Feigenbaum, Abyssinian St. 15, Jerusalem.
Secretary: Dr. E. Sinai, Tel Aviv.

Polish Ophthalmological Society

President: Dr. W. Kapuściński, 2 Waly Batorego, Poznań.
Secretary: Dr. J. Sobański, Lindley'a 4, Warsaw.
Place: Lindley'a 4, Warsaw.

Royal Society of Medicine, Section of Ophthalmology

President: Col. F. A. Juler, 96 Harley St., London, W. 1, England.
Secretary: Dr. Harold Ridley, 60 Queen Anne St., London, W. 1, England.

São Paulo Society of Ophthalmology

President: Silvio de Almeida Toledo, Barão de Ilapetininga St., 88, 5° Andar, São Paulo, Brazil.
Secretary: Dr. Plinio de Toledo Piza, Enfermaria Santo Luzia, Santa Casa de Misericordia, Cesario Motta, St. 112, São Paulo, Brazil.

Scottish Ophthalmological Club

President: Dr. S. Spence Meighan, 13 Woodside Pl., Glasgow, C. 3.
Secretary: Dr. Alexander Garrow, 15 Woodside Pl., Glasgow, C. 3.
Place: Edinburgh and Glasgow, in rotation.

Sociedad Argentina de Oftalmologia

Chairman: Dr. Jorge Malbrán, Buenos Aires.
Secretary: Dr. Benito Just Tiscornia, Santa Fe 1171, Buenos Aires.

Sociedad Oftalmologia del Litoral, Rosario (Argentina)

President: Prof. Dr. Carlos Weskamp, Laprida 1159, Rosario.
Secretary: Dr. Arturo Etchemendigaray, Villa Constitución, Santa Fé.
Place: Rosario. Time: Last Saturday of every month, April to November. All correspondence should be addressed to the President.

Sociedade de Oftalmología del Norte

President: Dr. Alberto Cárdenas.
Secretary: Dr. Jorge Luis Castillo, Mendoza 421, Tucumán, Argentina.

Sociedade de Oftalmologia de Minas Gerais

President: Prof. Hilton Rocha, Rua Rio de Janeiro 2251, Bello Horizonte, Minas Geraes, Brazil.
Secretary: Dr. Ennio Coscarelli, Rua Aimorés 1697, Bello Horizonte, Minas Geraes, Brazil.

Sociedade de Oftalmologia e Otorrinolaringologia de Rio Grande do Sul

President: Dr. Luiz Assumpção Osorio, Edificio Vera Cruz, Apartamento 134, Porto Alegre, Rio Grande do Sul.
Secretary: Dr. Fernando Voges Alves, Caixa Postal 928, Porto Alegre, Rio Grande do Sul.

SOCIEDADE DE OPHTHALMOLOGIA E OTO-RHINO-LARYNGOLOGIA DA BAHIA

President: Dr. Theonilo Amorim, Barra Avenida, Bahia, Brazil.
Secretary: Dr. Adroaldo de Alencar, Brazil.
All correspondence should be addressed to the President.

SOCIETÀ OFTALMOLOGICA ITALIANA

President: Prof. Dott. Giuseppe Ovio, Ophthalmological Clinic, University of Rome, Rome.
Secretary: Prof. Dott. Epimaco Leonardi, Via del Gianicolo, 1, Rome.

SOCIÉTÉ FRANÇAISE D'OPHTALMOLOGIE

Secretary: Dr. René Onfray, 6 Avenue de la Motte Picquet, Paris, 7e.

SOCIETY OF SWEDISH OPHTHALMOLOGISTS

President: Prof. K. G. Ploman, Stockholm.
Secretary: Dr. K. O. Granström, Södermalmstorg 4, III tr., Stockholm, Sö.

TEL AVIV OPHTHALMOLOGICAL SOCIETY

President: Dr. D. Arieh-Friedman, 96 Allenby St., Tel Aviv, Palestine.
Secretary: Dr. Sadger Max, 9 Bialik St., Tel Aviv, Palestine.

NATIONAL

AMERICAN MEDICAL ASSOCIATION, SCIENTIFIC ASSEMBLY, SECTION ON OPHTHALMOLOGY

Chairman: Dr. Frederick C. Cordes, 384 Post St., San Francisco.
Secretary: Dr. R. J. Masters, 23 E. Ohio St., Indianapolis.
Place: San Francisco. Time: July 1-5, 1946.

AMERICAN ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY, SECTION ON OPHTHALMOLOGY

President: Dr. Gordon B. New, Mayo Clinic, Rochester, Minn.
President-Elect: Dr. Alan C. Woods, Johns Hopkins Hospital, Baltimore 5.
Executive Secretary-Treasurer: Dr. William L. Benedict, 100–1st Ave. Bldg., Rochester, Minn.

AMERICAN OPHTHALMOLOGICAL SOCIETY

President: Dr. Eugene M. Blake, 303 Whitney Ave., New Haven, Conn.
Secretary-Treasurer: Dr. Walter S. Atkinson, 129 Clinton St., Watertown, N. Y.

ASSOCIATION FOR RESEARCH IN OPHTHALMOLOGY, INC.

Chairman: Dr. Conrad Berens, 35 E. 70th St., New York.
Secretary-Treasurer: Major Brittain F. Payne, School of Aviation Medicine, Randolph Field, Texas.
Assistant Secretary-Treasurer: Dr. Hunter Romaine, 35 E. 70th St., New York.

CANADIAN MEDICAL ASSOCIATION, SECTION ON OPHTHALMOLOGY

President: Dr. Alexander E. MacDonald, 170 St. George St., Toronto 5.
Secretary-Treasurer: Dr. L. J. Sebert, 170 St. George St., Toronto 5.

CANADIAN OPHTHALMOLOGICAL SOCIETY

President: Walter W. Wright, 170 St. George St., Toronto 5.
Secretary-Treasurer: Dr. Kenneth B. Johnston, Suite 1, 1509 Sherbrooke St. W., Montreal.

NATIONAL SOCIETY FOR THE PREVENTION OF BLINDNESS

President: Mr. Mason H. Bigelow, 1790 Broadway, New York.
Secretary: Miss Regina E. Schneider, 1790 Broadway, New York.
Executive Director: Mrs. Eleanor Brown Merrill, 1790 Broadway, New York.

SECTIONAL

ACADEMY OF MEDICINE OF NORTHERN NEW JERSEY, SECTION ON EYE, EAR, NOSE AND THROAT

President: Dr. N. Zwaifler, 46 Wilbur Ave., Newark.
Secretary: Dr. William F. Keim Jr., 25 Roseville Ave., Newark.
Place: 91 Lincoln Park South, Newark. Time: 8:45 p. m., second Monday of each month, October to May.

CENTRAL ILLINOIS SOCIETY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President: Dr. Watson Gailey, 1000 N. Main St., Bloomington, Ill.
Secretary-Treasurer: Dr. William F. Hubble, 861-867 Citizens Bldg., Decatur, Ill.

CENTRAL WISCONSIN SOCIETY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President: Dr. L. J. Friend, 425 E. Grand Ave., Beloit, Wis.
Secretary: Dr. G. L. McCormick, 626 S. Central Ave., Marshfield.

NEW ENGLAND OPHTHALMOLOGICAL SOCIETY

President: Dr. Theodore L. Terry, 140 Marlborough St., Boston.
Secretary-Treasurer: Dr. Merrill J. King, 264 Beacon St., Boston 16.
Place: Massachusetts Eye and Ear Infirmary, 243 Charles St., Boston. Time: 8 p. m., third Tuesday of each month from November to April, inclusive.

PACIFIC COAST OTO-OPHTHALMOLOGICAL SOCIETY

President: Dr. D. H. O'Rourke, 1612 Tremont Pl., Denver.
Secretary-Treasurer: Dr. C. Allen Dickey, 450 Sutter St., San Francisco.

PUGET SOUND ACADEMY OF OPHTHALMOLOGY AND OTO-LARYNGOLOGY

President: Dr. James H. Mathews, 1317 Marion St., Seattle, Wash.
Secretary-Treasurer: Dr. Barton E. Peden, 301 Stimson Bldg., Seattle 1.
Place: Seattle or Tacoma, Wash. Time: Third Tuesday of each month except June, July and August.

ROCK RIVER VALLEY EYE, EAR, NOSE AND THROAT SOCIETY

President: Dr. J. Sheldon Clark, 27 E. Stephenson St., Freeport, Ill.
Secretary-Treasurer: Dr. Harry R. Warner, 321 W. State St., Rockford, Ill.
Place: Rockford, Ill., or Janesville or Beloit, Wis. Time: Third Tuesday of each month from October to April, inclusive.

SAGINAW VALLEY ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President: Dr. L. D. Gomon, 308 Eddy Bldg., Saginaw, Mich.
Secretary-Treasurer: Dr. Harold H. Heuser, 207 Davidson Bldg., Bay City, Mich.
Place: Saginaw or Bay City, Mich. Time: Second Tuesday of each month, except July, August and September.

SIOUX VALLEY EYE AND EAR ACADEMY

President: Dr. J. C. Decker, 515 Francis Bldg., Sioux City, Iowa.
Secretary-Treasurer: Dr. J. E. Dvorak, 408 Davidson Bldg., Sioux City, Iowa.

SOUTHERN MEDICAL ASSOCIATION, SECTION ON EYE, EAR, NOSE AND THROAT

Chairman: Dr. John H. Burleson, 414 Navarro St., San Antonio, Texas.
Secretary: Dr. J. W. Jervey Jr., 101 Church St., Greenville, S. C.

SOUTHWESTERN ACADEMY OF EYE, EAR, NOSE AND THROAT

President: Dr. H. L. Brehmer, 221 W. Central Ave., Albuquerque, N. Mex.
Secretary: Dr. A. E. Cruthirds, 1011 Professional Bldg., Phoenix, Ariz.

SOUTHWESTERN MICHIGAN TRIOLOGICAL SOCIETY

President: Dr. W. M. Dodge, 716 First National Bank Bldg., Battle Creek.
Secretary-Treasurer: Dr. Kenneth Lowe, 25 W. Michigan Ave., Battle Creek.
Time: Last Thursday of September, October, November, March, April and May.

WESTERN PENNSYLVANIA EYE, EAR, NOSE AND THROAT SOCIETY

President: Dr. Ray Parker, 218 Franklin St., Johnstown, Pa.
Secretary-Treasurer: Dr. J. McClure Tyson, Deposit National Bank Bldg., Dubois.

STATE

ARKANSAS STATE MEDICAL SOCIETY, EYE, EAR, NOSE AND THROAT SECTION

President: Dr. Raymond C. Cook, 701 Main St., Little Rock.
Secretary: Dr. K. W. Cosgrove, Urquhart Bldg., Little Rock.

COLORADO OPHTHALMOLOGICAL SOCIETY

President: Dr. C. A. Ringle, 912–9th Ave., Greeley.
Secretary: Dr. W. A. Ohmart, 1102 Republic Bldg., Denver.
Place: University Club, Denver. Time: 7:30 p. m., third Saturday of each month, October to May, inclusive.

CONNECTICUT STATE MEDICAL SOCIETY, SECTION ON EYE, EAR, NOSE AND THROAT

President: Dr. F. L. Phillips, 405 Temple St., New Haven.
Secretary-Treasurer: Dr. W. H. Turnley, 1 Atlantic St., Stamford, Conn.

EYE, EAR, NOSE AND THROAT CLUB OF GEORGIA

President: Dr. William O. Martin Jr., Doctors Bldg., Atlanta.
Secretary-Treasurer: Dr. C. K. McLaughlin, 526 Walton St., Macon.

INDIANA ACADEMY OF OPHTHALMOLOGY AND OTO-LARYNGOLOGY

President: Dr F. McK. Ruby, Union City.
Secretary: Dr. Edwin W. Dyar Jr., 23 E. Ohio St., Indianapolis.
Place: French Lick. Time: First Wednesday in April.

IOWA ACADEMY OF OPHTHALMOLOGY AND OTO-LARYNGOLOGY

President: Dr. J. K. Von Lackum, 117–3d St. S. E., Cedar Rapids.
Secretary-Treasurer: Dr. B. M. Merkel, 604 Locust St., Des Moines.

KANSAS STATE MEDICAL SOCIETY, SECTION ON OPHTHALMOLOGY AND OTOLARYNGOLOGY

President: Dr. W. D. Pittman, Pratt.
Secretary: Dr. Louis R. Haas, 902 N. Broadway, Pittsburg.

LOUISIANA-MISSISSIPPI OPHTHALMOLOGICAL AND OTOLARYNGOLOGICAL SOCIETY

President: Dr. Val H. Fuchs, 200 Carondelet St., New Orleans.
Secretary-Treasurer: Dr. Edley H. Jones, 1301 Washington St., Vicksburg, Miss.

MEDICAL SOCIETY OF THE STATE OF PENNSYLVANIA, SECTION ON EYE, EAR, NOSE AND THROAT DISEASES

Chairman: Dr. William T. Hunt Jr., 1205 Spruce St., Philadelphia 7.
Secretary: Dr. Gabriel Tucker, 250 S. 18th St., Philadelphia 3.

MICHIGAN STATE MEDICAL SOCIETY, SECTION OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

Chairman: Dr. Edmond L. Cooper, 1553 Woodward Ave., Detroit 26.
Secretary: Dr. Ralph H. Gilbert, 110 Fulton St. E., Grand Rapids.

MINNESOTA ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President: Dr. Karl C. Wold, 1051 Lowry Bldg., St. Paul 2.
Secretary: Dr. William A. Kennedy, 372 St. Peter St., St. Paul 2.
Time: Second Friday of each month from October to May.

MONTANA ACADEMY OF OTO-OPHTHALMOLOGY

President: Dr. William Morrison, 208 N. Broadway, Billings.
Secretary: Dr. Fritz D. Hurd, 309 Medical Arts Bldg., Great Falls.

NEBRASKA ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President: Dr. W. Howard Morrison, 1500 Medical Arts Bldg., Omaha.
Secretary-Treasurer: Dr. John Peterson, 1307 N St., Lincoln.

NEW JERSEY STATE MEDICAL SOCIETY, SECTION ON OPHTHALMOLOGY, OTOLOGY AND RHINOLARYNGOLOGY

Chairman: Dr. George P. Meyer, 410 Haddon Ave., Camden.
Secretary: Dr. John P. Brennan, 429 Cooper St., Camden.

NEW YORK STATE MEDICAL SOCIETY, EYE, EAR, NOSE AND THROAT SECTION

Chairman: Dr. Harold J. Joy, 504 State Tower Bldg., Syracuse 2.
Secretary: Dr. Maxwell D. Ryan, 660 Madison Ave., New York 21.

NORTH CAROLINA EYE, EAR, NOSE AND THROAT SOCIETY

President: Dr. Hugh C. Wolfe, 102 N. Elm St., Greensboro.
Secretary: Dr. Vanderbilt F. Couch, 104 W. 4th St., Winston-Salem.

NORTH DAKOTA ACADEMY OF OPHTHALMOLOGY AND OTO-LARYNGOLOGY

President: Dr. W. L. Diven, City National Bank Bldg., Bismarck.
Secretary-Treasurer: Dr. A. E. Spear, 20 W. Villard, Dickenson.

OREGON ACADEMY OF OPHTHALMOLOGY AND OTO-LARYNGOLOGY

President: Dr. Paul Neely, 1020 S. W. Taylor St., Portland.
Secretary-Treasurer: Dr. Harold M. U'Ren, 624 Medical Arts Bldg., Portland 5.
Place: Good Samaritan Hospital, Portland. Time: Third Tuesday of each month.

PENNSYLVANIA ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President: Dr. Lewis T. Buckman, 83 S. Franklin St., Wilkes-Barre.
Secretary Pro Tem: Dr. Paul C. Craig, 232 N. 5th St., Reading.
Time: Last week in April.

RHODE ISLAND OPHTHALMOLOGICAL AND OTOLOGICAL SOCIETY

Acting President: Dr. N. Darrell Harvey, 112 Waterman St., Providence.
Secretary-Treasurer: Dr. Linley C. Happ, 124 Waterman St., Providence.
Place: Rhode Island Medical Society, Library, Providence. Time: 8:30 p. m., second Thursday in October, December, February and April.

SOUTH CAROLINA SOCIETY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President: Dr. J. H. Stokes, 125 W. Cheves St., Florence.
Secretary-Treasurer: Dr. Roderick Macdonald, 330 E. Main St., Rock Hill.

TENNESSEE ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President: Dr. Wesley Wilkerson, 700 Church St., Nashville.
Secretary-Treasurer: Dr. W. D. Stinson, 124 Physicians and Surgeons Bldg., Memphis.

TEXAS OPHTHALMOLOGICAL AND OTO-LARYNGOLOGICAL SOCIETY

President: Dr. F. H. Rosebrough, 603 Navarro St., San Antonio.
Secretary: Dr. M. K. McCullough, 1717 Pacific Ave., Dallas.

UTAH OPHTHALMOLOGICAL SOCIETY

President: Dr. E. B. Fairbanks, 315 Medical Arts Bldg., Salt Lake City.
Secretary-Treasurer: Dr. Dean Spear, 516 Boston Bldg., Salt Lake City.
Place: University Club, Salt Lake City. Time: 7:00 p. m., third Monday of each month.

VIRGINIA SOCIETY OF OTO-LARYNGOLOGY AND OPHTHALMOLOGY

President: Dr. Mortimer H. Williams, 30½ Franklin Rd. S. W., Roanoke.
Secretary-Treasurer: Dr. Meade Edmunds, 34 Franklin St., Petersburg.

WEST VIRGINIA STATE MEDICAL ASSOCIATION, EYE, EAR, NOSE AND THROAT SECTION

President: Dr. George Traugh, 309 Cleveland Ave., Fairmont.
Secretary: Dr. Welch England, 621½ Market St., Parkersburg.

LOCAL

AKRON ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President: Dr. E. L. Mather, 39 S. Main St., Akron, Ohio.
Secretary-Treasurer: Dr. V. C. Malloy, 2d National Bank Bldg., Akron, Ohio.
Time: First Monday in January, March, May and November.

ATLANTA EYE, EAR, NOSE AND THROAT SOCIETY

President: Dr. B. M. Cline, 153 Peachtree St. N. E., Atlanta, Ga.
Acting Secretary: Dr. A. V. Hallum, 478 Peachtree St. N. E., Atlanta, Ga.
Place: Grady Hospital. Time: 6:00 p. m., fourth Monday of each month from October to May.

BALTIMORE MEDICAL SOCIETY, SECTION ON OPHTHALMOLOGY

Chairman: Dr. Ernst Bodenheimer, 1212 Eutaw Pl., Baltimore.
Secretary: Dr. Thomas R. O'Rourk, 104 W. Madison St., Baltimore.
Place: Medical and Chirurgical Faculty, 1211 Cathedral St. Time: 8:30 p. m., fourth Thursday of each month from October to March.

Birmingham Eye, Ear, Nose and Throat Club

President: Each member, in alphabetical order.
Secretary: Dr. Luther E. Wilson, 919 Woodward Bldg., Birmingham, Ala.
Place: Tutwiler Hotel. Time: 6:30 p. m., second Tuesday of each month, September to May, inclusive.

Brooklyn Ophthalmological Society

President: Dr. Michael J. Buonaguro, 589 Lorimer St., Brooklyn 11.
Secretary-Treasurer: Dr. Louis Freimark, 256 Rochester Ave., Brooklyn 13.
Place: Kings County Medical Society Bldg., 1313 Bedford Ave. Time: Third Thursday in February, April, May, October and December.

Buffalo Ophthalmologic Club

President: Dr. William H. Howard, 389 Linwood Ave., Buffalo 9.
Secretary-Treasurer: Dr. Sheldon B. Freeman, 196 Linwood Ave., Buffalo 9.
Time: Second Thursday of each month from October to May.

Chattanooga Society of Ophthalmology and Otolaryngology

President: Each member, in alphabetical order.
Secretary: Dr. Douglas Chamberlain, Chattanooga Bank Bldg., Chattanooga, Tenn.
Place: Mountain City Club. Time: Second Thursday of each month from September to May.

Chicago Ophthalmological Society

President: Dr. Samuel J. Meyer, 58 E. Washington St., Chicago 2.
Secretary: Dr. W. A. Mann, 30 N. Michigan Ave., Chicago 2.
Place: Continental Hotel, 505 N. Michigan Ave. Time: Third Monday of each month from October to May.

Cincinnati General Hospital Ophthalmology Staff

Chairman: Dr. D. T. Vail, 441 Vine St., Cincinnati.
Secretary: Dr. A. A. Levin, 441 Vine St., Cincinnati.
Place: Cincinnati General Hospital. Time: 7:45 p. m., third Friday of each month except June, July and August.

Cleveland Ophthalmological Club

Chairman: Dr. M. Paul Motto, Rose Bldg., Cleveland.
Secretary: Dr. H. H. Wygand, Guardian Bldg., Cleveland.
Time: Second Tuesday in October, December, February and April.

College of Physicians, Philadelphia, Section on Ophthalmology

Chairman: Dr. W. S. Reese, 1901 Walnut St., Philadelphia.
Clerk: Dr. George F. J. Kelly, 37 S. 20th St., Philadelphia.
Time: Third Thursday of every month from October to April, inclusive.

Columbus Ophthalmological and Oto-Laryngological Society

Chairman: Dr. Erwin W. Troutman, 21 E. State St., Columbus, Ohio.
Secretary-Treasurer: Dr. T. Rees Williams, 380 E. Town St., Columbus 15, Ohio.
Place: University Club. Time: 6:15 p. m., first Monday of each month, from October to May, inclusive.

Corpus Christi Eye, Ear, Nose and Throat Society

Chairman: Dr. C. B. Collins, 704 Medical Professional Bldg., Corpus Christi, Texas.
Secretary: Dr. L. W. O. Janssen, 710 Medical Professional Bldg., Corpus Christi, Texas.
Time: 6:30 p. m., third Tuesday of each month from October to May.

Dallas Academy of Ophthalmology and Oto-Laryngology

President: Dr. Ruby K. Daniel, Medical Arts Bldg., Dallas 1, Texas.
Secretary: Dr. Tom Barr, Medical Arts Bldg., Dallas 1, Texas.
Place: Dallas Athletic Club. Time: 6:30 p. m., first Tuesday of each month from October to June. The November, January and March meetings are devoted to clinical work.

Des Moines Academy of Ophthalmology and Otolaryngology

President: Dr. H. C. Schmitz, 604 Locust St., Des Moines, Iowa.
Secretary-Treasurer: Dr. Byron M. Merkel, 604 Locust St., Des Moines, Iowa.
Time: 7:45 p. m., third Monday of every month from September to May.

Detroit Ophthalmological Club

Chairman: Members rotate alphabetically.
Secretary: Dr. Wesley G. Reid, 667 Fisher Bldg., Detroit 2.
Place: Club rooms of Wayne County Medical Society. Time: First Monday of each month, November to April, inclusive.

Detroit Ophthalmological Society

President: Dr. Raymond S. Goux, 545 David Whitney Bldg., Detroit 26.
Secretary: Dr. Arthur Hale, 1609 Eaton Tower, Detroit 26.
Place: Club rooms of Wayne County Medical Society. Time: 6:30 p. m., third Thursday of each month from November to April, inclusive.

Eastern New York Eye, Ear, Nose and Throat Association

President: Appointed at each meeting.
Secretary-Treasurer: Dr. Joseph L. Holohan, 330 State St., Albany.
Time: Third Wednesday in October, November, March, April, May and June.

Fort Worth Eye, Ear, Nose and Throat Society

President: Dr. Rex Howard, 602 W. 10th St., Fort Worth, Texas.
Secretary-Treasurer: Dr. R. H. Gough, Medical Arts Bldg., Fort Worth, Texas.
Place: Medical Hall, Medical Arts Bldg. Time: 7:30 p. m., first Friday of each month except July and August.

Houston Academy of Medicine, Ophthalmological and Oto-Laryngological Section

President: Dr. Lyle J. Logue, 1304 Walker Ave., Houston, Texas.
Secretary: Dr. John T. Stough, 803 Medical Arts Bldg., Houston, Texas.
Place: Medical Arts Bldg., Harris County Medical Society Rooms. Time: 8 p. m., second Thursday of each month from September to June.

Indianapolis Ophthalmological and Otolaryngological Society

President: Dr. Myron Harding, 23 E. Ohio St., Indianapolis.
Secretary: Dr. Kenneth L. Craft, 23 E. Ohio St., Indianapolis.
Place: Indianapolis Athletic Club. Time: 6:30 p. m., second Thursday of each month from November to May.

Kansas City Society of Ophthalmology and Oto-Laryngology

President: Dr. Edgar Johnson, 906 Grand Ave., Kansas City, Mo.
Secretary: Dr. W. E. Keith, 1103 Grand Ave., Kansas City, Mo.
Time: Third Thursday of each month from October to June. The November, January and March meetings are devoted to clinical work.

Long Beach Eye, Ear, Nose and Throat Society

Chairman: Dr. Francis Carl Hertzog, 117 E. 8th St., Long Beach, Calif.
Secretary-Treasurer: Dr. Robert G. Thornburgh, 117 E. 8th St., Long Beach, Calif.
Place: Seaside Hospital. Time: Last Wednesday of each month from October to May.

Los Angeles Society of Ophthalmology and Otolaryngology

President: Dr. Orrie E. Ghrist, 210 N. Central Ave., Glendale, Calif.
Secretary-Treasurer: Dr. K. C. Brandenburg, 110 Pine Ave., Long Beach 2, Calif.
Place: Los Angeles County Medical Association Bldg., 1925 Wilshire Blvd. Time: 6:30 p. m., fourth Monday of each month from September to May, inclusive.

Louisville Eye and Ear Society

President: Dr. Joseph S. Heitger, Heyburn Bldg., Louisville, Ky.
Secretary-Treasurer: Dr. J. W. Fish, 321 W. Broadway, Louisville, Ky.
Place: Brown Hotel. Time: 6:30 p. m., second Thursday of each month from September to May, inclusive.

Lower Anthracite Eye, Ear, Nose and Throat Society

Chairman: Each member in alphabetical order.
Secretary: Dr. James J. Monohan, 31 S. Jardin St., Shenandoah, Pa.

Medical Society of the District of Columbia, Section of Ophthalmology and Otolaryngology

Chairman: Dr. P. S. Constantinople, 1835 I St. N. W., Washington.
Secretary: Dr. Frazier Williams, 1801 I St. N. W., Washington.
Place: 1718 M St. N. W. Time: 8 p. m., third Friday of each month from October to April, inclusive.

Memphis Society of Ophthalmology and Otolaryngology

Chairman: Each member, in alphabetical order.
Secretary: Dr. Sam H. Sanders, 1089 Madison Ave., Memphis, Tenn.
Place: Eye Clinic of Memphis Eye, Ear, Nose and Throat Hospital. Time: 8 p. m., second Tuesday of each month from September to May.

Milwaukee Oto-Ophthalmic Society

President: Dr. Ralph T. Rank, 238 W. Wisconsin Ave., Milwaukee.
Secretary-Treasurer: Dr. Frank G. Treskow, 411 E. Mason St., Milwaukee 2.
Place: University Club. Time: 6:30 p. m., fourth Tuesday of each month from October to May.

Montgomery County Medical Society

Chairman: Dr. H. V. Dutrow, 1040 Fidelity Medical Bldg., Dayton, Ohio.
Secretary-Treasurer: Dr. Maitland D. Place, 981 Reibold Bldg., Dayton, Ohio.
Place: Van Cleve Hotel. Time: 6:30 p. m., first Tuesday of each month from October to June, inclusive.

Montreal Ophthalmological Society

President: Dr. J. Rosenbaum, 1396 Ste. Catherine St. W., Montreal, Canada.
Secretary: Dr. L. Tessier, 1230 St. Joseph Blvd. E., Montreal, Canada.
Time: Second Thursday of October, December, February and April.

Nashville Academy of Ophthalmology and Otolaryngology

Chairman: Dr. M. M. Cullom, 700 Church St., Nashville, Tenn.
Secretary: Dr. R. E. Sullivan, 432 Doctors Bldg., Nashville, Tenn.
Place: James Robertson Hotel. Time: 6:30 p. m., third Monday of each month from October to May.

NEW HAVEN OPHTHALMOLOGICAL SOCIETY

President: Dr. William H. Ryder, 185 Church St., New Haven, Conn.
Secretary: Dr. Frederick A. Wiess, 255 Bradley St., New Haven, Conn.

NEW ORLEANS OPHTHALMOLOGICAL AND OTOLARYNGOLOGICAL SOCIETY

President: Dr. W. B. Clark, 1012 American Bank Bldg., New Orleans.
Secretary: Dr. Mercer G. Lynch, 1018 Maison Blanche Bldg., New Orleans.
Place: Louisiana State University Medical Bldg. Time: 8 p. m., second Tuesday of each month from October to May.

NEW YORK ACADEMY OF MEDICINE, SECTION OF OPHTHALMOLOGY

Chairman: Dr. Rudolf Aebli, 30 E. 40th St., New York.
Secretary: Dr. Truman L. Boyes, 654 Madison Ave., New York.
Time: 8:30 p. m., third Monday of every month from October to May, inclusive.

NEW YORK SOCIETY FOR CLINICAL OPHTHALMOLOGY

President: Dr. Maurice L. Wieselthier, 1322 Union St., Brooklyn.
Secretary: Dr. Benjamin Esterman, 983 Park Ave., New York 28.
Place: New York Academy of Medicine, 2 E. 103d St. Time: 8 p. m., first Monday of each month from October to May, inclusive.

OKLAHOMA CITY ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President: Dr. Harvey O. Randel, 117 N. Broadway, Oklahoma City.
Secretary: Dr. S. R. Shaver, 117 N. Broadway, Oklahoma City.
Place: University Hospital. Time: Second Tuesday of each month from September to May.

OMAHA AND COUNCIL BLUFFS OPHTHALMOLOGICAL AND OTO-LARYNGOLOGICAL SOCIETY

President: Dr. A. A. Steinberg, 1502 Farnam St., Omaha.
Secretary-Treasurer: Dr. W. Howard Morrison, 1500 Medical Arts Bldg., Omaha 2.
Place: Omaha Club, 20th and Douglas Sts., Omaha. Time: 6 p. m. dinner; 7 p. m. program; third Wednesday of each month from October to May.

PASSAIC-BERGEN OPHTHALMOLOGICAL CLUB

President: Dr. Thomas Sanfacon, 340 Park Ave., Paterson, N. J.
Secretary-Treasurer: Dr. J. Averbach, 435 Clinton Ave., Clinton, N. J.
Place: Paterson Eye and Ear Infirmary. Time: 9 p. m., last Friday of every month, except June, July and August.

PHILADELPHIA COUNTY MEDICAL SOCIETY, EYE SECTION

President: Dr. Isaac Tassman, 136 S. 16th St., Philadelphia.
Secretary: Dr. Glen Gregory Gibson, 255 S. 17th St., Philadelphia.
Time: First Thursday of each month from October to May.

PITTSBURGH OPHTHALMOLOGICAL SOCIETY

President: Dr. Clarence F. Bernatz, Park Bldg., Pittsburgh.
Secretary: Dr. Robert J. Billings, Park Bldg., Pittsburgh.
Place: Pittsburgh Academy of Medicine Bldg. Time: Fourth Monday of each month, except June, July, August and September.

READING EYE, EAR, NOSE AND THROAT SOCIETY

President: Dr. Isaac B. High, 326 N. 5th St., Reading, Pa.
Secretary: Dr. Paul C. Craig, 232 N. 5th St., Reading, Pa.
Place: Wyomissing Club. Time: 6:30 p. m., third Wednesday of each month from September to July.

RICHMOND EYE, EAR, NOSE AND THROAT SOCIETY

President: Dr. Luther C. Brawner, Professional Bldg., Richmond, Va.
Secretary: Dr. Clifford A. Folkes, Professional Bldg., Richmond, Va.
Place: Westmoreland Club. Time: 6 p. m., second Monday of each month from October to May.

ROCHESTER EYE, EAR, NOSE AND THROAT SOCIETY

President: Dr. Frank Barber, 75 S. Fitzhugh St., Rochester, N. Y.
Secretary-Treasurer: Dr. Charles T. Sullivan, 277 Alexander St., Rochester, N. Y.

ST. LOUIS OPHTHALMIC SOCIETY

President: Dr. Vincent Jones, 634 N. Grand Blvd., St. Louis.
Secretary: Dr. T. E. Sanders, 508 N. Grand Blvd., St. Louis 3.
Place: Oscar Johnson Institute. Time: Fourth Friday of each month from October to April, inclusive, except December, at 8:00 p. m.

SAN ANTONIO OPHTHALMO-OTO-LARYNGOLOGICAL SOCIETY

President: Dr. Belvin Pritchett, 705 E. Houston St., San Antonio 5, Texas.
Secretary-Treasurer: Lt. Col. John L. Matthews, AAF School of Aviation Medicine, Randolph Field, Texas.
Place: San Antonio, Brooke General Hospital, Randolph Field or San Antonio Aviation Cadet Center. Time: 7 p. m., second Tuesday of each month from October to May.

SAN FRANCISCO COUNTY MEDICAL SOCIETY, SECTION ON EYE, EAR, NOSE AND THROAT

Chairman: Dr. Roy H. Parkinson, 870 Market St., San Francisco.
Secretary: Dr. A. G. Rawlins, 384 Post St., San Francisco.
Place: Society's Bldg., 2180 Washington St., San Francisco. Time: Fourth Tuesday of every month except June, July and December.

SHREVEPORT EYE, EAR, NOSE AND THROAT SOCIETY

President: Dr. David C. Swearingen, Slattery Bldg., Shreveport, La.
Secretary-Treasurer: Dr. Kenneth Jones, Medical Arts Bldg., Shreveport, La.
Place: Shreveport Charity Hospital. Time: 7:30 p. m., first Monday of every month except July, August and September.

SPOKANE ACADEMY OF OPHTHALMOLOGY AND OTO-LARYNGOLOGY

President: Dr. Clarence A. Veasey Sr., 421 W. Riverside Ave., Spokane, Wash.
Secretary: Dr. Clarence A. Veasey, 421 W. Riverside Ave., Spokane, Wash.
Place: Spokane Medical Library. Time: 8 p. m., fourth Tuesday of each month except June, July and August.

SYRACUSE EYE, EAR, NOSE AND THROAT SOCIETY

President: Dr. A. H. Rubenstein, 713 E. Genesee St., Syracuse, N. Y.
Secertary-Treasurer: Dr. I. H. Blaisdell, 713 E. Genesee St., Syracuse, N. Y.
Place: University Club. Time: First Tuesday of each month except June, July and August.

TOLEDO EYE, EAR, NOSE AND THROAT SOCIETY

Chairman: Dr. L. C. Ravin, 316 Michigan St., Toledo 2, Ohio.
Secretary: Dr. W. W. Randolph, 1838 Parkwood Ave., Toledo, Ohio.
Place: Toledo Club. Time: Each month except June, July and August.

TORONTO ACADEMY OF MEDICINE, SECTION OF OPHTHALMOLOGY

Chairman: Dr. W. R. F. Luke, 316 Medical Arts Bldg., Toronto, Canada.
Secretary: Dr. W. T. Gratton, 216 Medical Arts Bldg., Toronto, Canada.
Place: Academy of Medicine, 13 Queens Park. Time: First Monday of each month, November to April.

WASHINGTON, D. C., OPHTHALMOLOGICAL SOCIETY

President: Dr. Harold M. Downey, 1740 M St. N. W., Washington, D. C.
Secretary-Treasurer: Dr. Richard W. Wilkinson, 1408 L St. N. W., Washington, D. C.
Place: Medical Society of District of Columbia Bldg., 1718 M St. N. W., Washington, D. C. Time: 7:30 p. m., first Monday in November, January, March and May.

WILKES-BARRE OPHTHALMOLOGICAL SOCIETY

Chairman: Each member in turn.
Secretary: Dr. Samuel T. Buckman, 70 S. Franklin St., Wilkes-Barre, Pa.
Place: Office of chairman. Time: Last Tuesday of each month from October to May.